

(19)



Europäisches Patentamt
European Patent Office
Office européen des brevets



(11) EP 0 530 537 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
08.01.1997 Bulletin 1997/02

(51) Int Cl. 6: C07D 487/04, C07D 495/04,
C07D 491/048, A61K 31/505
// (C07D487/04, 239:00,
209:00),
(C07D495/04, 333:00, 239:00),
(C07D491/048, 307:00, 239:00)

(21) Application number: 92113523.2

(22) Date of filing: 07.08.1992

(54) Condensed pyrimidine derivatives, their production and use as antitumor agents

Kondensierte Pyrimidinderivate, ihre Herstellung und ihre Verwendung als Antitumormittel

Dérivés de la pyrimidine condensés, leur préparation et leur utilisation comme agents antitumoraux

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL PT
SE

- Ootsu, Koichiro
Mishima-gun, Osaka 618 (JP)
- Itoh, Fumio
Toyonaka, Osaka 560 (JP)

(30) Priority: 12.08.1991 JP 202042/91
27.03.1992 JP 71513/92
05.06.1992 JP 145851/92

(74) Representative:
von Kreisler, Alek, Dipl.-Chem. et al
Patentanwälte
von Kreisler-Selting-Werner
Postfach 10 22 41
50462 Köln (DE)

(43) Date of publication of application:
10.03.1993 Bulletin 1993/10

(56) References cited:
EP-A- 0 239 362 EP-A- 0 438 261

(73) Proprietor: TAKEDA CHEMICAL INDUSTRIES,
LTD.
Chuo-ku, Osaka 541 (JP)

(72) Inventors:
• Akimoto, Hiroshi
Kobe, Hyogo 658 (JP)

USSN: 10/619,662 FILED: 07/15/2003
PC25132A

EP 0 530 537 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give notice to the European Patent Office of opposition to the European patent granted. Notice of opposition shall be filed in a written reasoned statement. It shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

Description

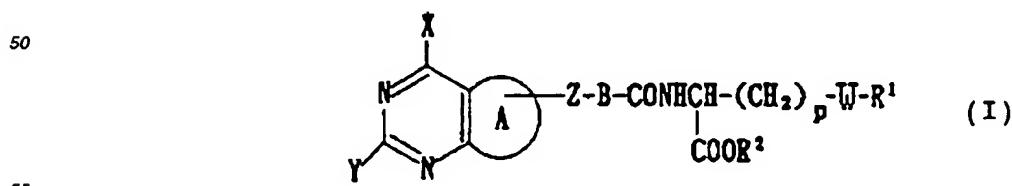
This invention relates to a novel condensed pyrimidine derivative useful as an anti-tumor agent, its production and use.

5 Folic acid and its related compounds are carriers of a C1 unit in a living body, derived from formic acid or formaldehyde, acting as a coenzyme in various enzymatic reactions such as those in biosynthesis of nucleic acid, in metabolism of amino acids and peptides and in generation of methane. Particularly for metabolism and transition reaction of C1 units in biosynthesis of nucleic acid, i.e. the purine synthetic pathway and the thymidine synthetic pathway, folic acid and its related compounds are essential. In order for folic acid to demonstrate its biological activities, normally, it
 10 is required to undergo two steps of reduction to be transformed into its active coenzyme form. As a drug substance which binds strongly to the enzyme (dihydrofolate reductase : DHFR) governing the second reduction step to thereby inhibit the reduction of dihydrofolate to tetrahydrofolate, there are known amethopterine (methotrexate: MTX) and its analogous compounds. These drugs, that act to exert damage to DNA synthesis, eventually bringing about cell death, have been developed as an antitumor agent and occupy a clinically important position as therapeutic agent of, mainly,
 15 leukemia. Furthermore, with remarkable developments of research work in the field of biochemistry, especially in the field of folic acid and relating compounds for the therapy of cancers, reports have been made of a novel DHFR inhibitor, namely a 10-deazaaminopterin-based antitumor agent (10-ethyl-10-deazaaminopterin: 10-EDAM) [NCI Monograph, 5, 127 (1987)] or an aminopteroyl type ornithine derivative, namely an N(α)-(4-amino-4-deoxypteroyl)-N(δ)-hemipthaloyl-L-ornithine: PT523 [Japanese Publish unexamined Patent Application No. 502095/1990], and an antagonism
 20 inhibiting agent aiming at an enzyme different from DHFR, namely a 5-deazatetrahydro folic acid-based antitumor agent, which can act principally through a mechanism to inhibit glycinamideribonucleotide transformylase, namely 5,10-dideaza-5,6,7,8-tetrahydro folic acid: DDATHF [Journal of Medicinal Chemistry, 28, 914(1985)] or a quinazoline-based antitumor agent, which can work principally through a mechanism to inhibit thymidylate synthetase (2-desamino-2-methyl-10-propargyl-5,8-dideazafolate: DMPDDF) [British Journal of Cancer, 58, 241 (1988)]. All of these compounds
 25 are, however, within the category of heterocyclic compounds having a basic skeleton of a condensed ring of 6-membered rings (6-6 condensed ring). On the other hand, it was also reported that the folic acid antagonistic agents having the pyrrolo[2,3-d] pyrimidine ring as the basic skeleton which is a condensed ring from a 6-membered ring and a 5-membered ring has excellent antitumor activity, as well. However, there has been described that it is essential for the above-mentioned pyrrolo[2,3-d]pyrimidine derivatives to have glutamic acid mainly at the terminal side chain
 30 [USP4,997,838, EP-A-400,562, EP-A-402,903, EP-A-418,924, EP-A-431,953, EP-A-434,426, EP-A-438,261 and USP4,996,206].

What is now specifically desired in the field of cancer therapy is the creation of drugs which have toxicities highly specific to cancer cells based on the action mechanism having excellent therapeutic effects. The MTX whose principal action mechanism consists in inhibition of dihydrofolate reductase is clinically used widely, though the therapeutic effect
 35 is still unsatisfactory because it has relatively strong toxicity with little effect on solid cancer. Further, acquired resistance against MTX has now been taken up as a great problem. As the resistance mechanism against MTX, there are counted, for example, rise of DHFR level, lowering of cell membrane capability of carrying drugs and lowering of the level of folylpolyglutamate synthetase (FPGS). By overcoming at least one of these resistance factors, development of drugs showing excellent therapeutic effect against MTX-resistant cancers has been expected.

40 This invention provides a novel condensed heterocyclic compounds which have not only 6-5 condensed ring as the basic skeleton but also, at the terminal side-chain, no two coexisting carboxyl groups derived from glutamic acid inhibit not less than one of the enzymatic reactions involving folic acid, exhibit highly selective toxicity against various tumors (especially human lung cancer cells) and also produce excellent antitumor effect which also overcome MTX-resistance.

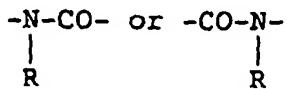
45 This inventors of present invention explored compounds which could be of use as medicament for inhibiting tumor and particularly compounds of value for inhibiting cell-proliferation and succeeded in the creation of a condensed pyrimidine derivative of the formula (I):



wherein the ring A stands for an optionally hydrogenated 5-membered ring optionally having substituents; B stands for an optionally substituted divalent 5- or 6-membered homo- or hetero-cyclic group; X stands for an amino group,

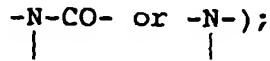
hydroxyl group or mercapto group; Y stands for hydrogen atom, halogen atom or a group bonded through carbon, nitrogen, oxygen or sulfur atom; Z stands for an optionally substituted divalent aliphatic group having five or less atoms constituting the straight-chain optionally including one heteroatom; W stands for a group represented by

5



- 10 (wherein R stands for a hydrogen atom or an optionally substituted C₁₋₄ hydrocarbon group or may form a 3-to 13-membered ring with R₁, taken together with adjacent

15



R₁ stands for an optionally substituted cyclic or chain-like group; COOR² stands for an optionally esterified carboxyl group; and p denotes an integer of 1 to 4 provided that when -W-R¹ denotes a moiety represented by the formula:

20

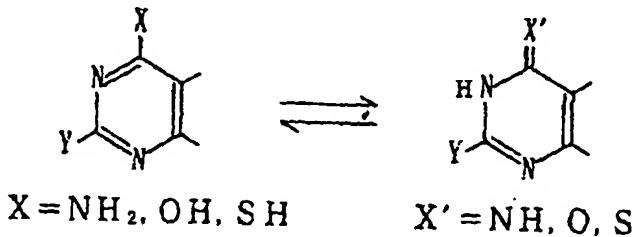


- 25 wherein COOR¹⁶ and COOR¹⁷ are, independently, an optionally esterified carboxyl group and n denotes an integer of 1 to 5, p denotes 1, 3 or 4, or its salt.

In the above formulae, the compounds of this invention can exist as an equilibrium mixture with their tautomeric isomers. Illustrated below are the partial structural formulae capable of undergoing tautomerism, with the equilibria among them being shown as well.

30

35

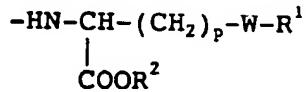


40

Throughout this specification, for the purpose of convenience of expression, the amino, hydroxyl and mercapto forms are to be described, with the corresponding designations being adopted, and in either case, their tautomers or the imino, oxo and thioxo forms are understood to be included in the scope of this invention.

- 45 And, in the compounds of this invention, the presence of a plural number of asymmetric centers is possible, but except that the absolute configuration of the partial structural formula:

50



55

is S(L), the absolute configurations of other asymmetric centers may be either of S, R or a mixture of RS. In such a case, a plurality of diastereomers exist, and they can be easily separated by conventional purification means, if necessary.

All the above-described diastereomers that can be separated by such procedures are included in the scope of this invention.

Referring to the above formulae, the 5-membered rings of optionally hydrogenated 5-membered rings shown by

the ring A include, for example, 5-membered rings being composed of carbon atoms alone or both carbon atoms and one hetero atom (for example, optionally oxidized nitrogen atom, oxygen atom or optionally oxidized sulfur atom). Examples of such optionally hydrogenated 5-membered rings include a cyclopentadiene, cyclopentene, furan, dihydrofuran, thiophene, dihydrothiophene, thiophen-1-oxide, dihydrothiophen-1-oxide, thiophene-1,1-dioxide, dihydrothiophene-1,1-dioxide, pyrrole, pyrrolidine and so on. The more preferable examples include a pyrrole, furan, thiophene and so on. These 5-membered rings may have one or two substituents at their replaceable, and examples of such substituents include C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl group), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl, propargyl group), C₃₋₈ cycloalkyl group (e.g. cyclopropyl group), halogen atom (e.g. fluorine, chlorine, bromine, iodine), C₁₋₄ alkanoyl group (e.g. formyl, 10 acetyl, propionyl, butyryl, isobutyryl group), benzoyl group, substituted benzoyl group (e.g. halogenobenzoyl group such as p-chlorobenzoyl, p-methoxybenzoyl or 3,4,5-trimethoxybenzoyl group, or mono-, di- or tri-C₁₋₄ alkoxy benzoyl), cyano group, carboxyl group, carbamoyl group, nitro group, hydroxyl group, hydroxy-C₁₋₄ alkyl group (e.g. methoxymethyl group, ethoxymethyl group, methoxyethyl group, ethoxyethyl group), C₁₋₄ alkoxy-C₁₋₄ alkyl (e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl) C₁₋₄ alkoxy group (e.g. methoxy, ethoxy, propoxy group), mercapto group, 15 C₁₋₄ alkylthio group (e.g. methylthio, ethylthio, propylthio group), amino group, mono- or di-C₁₋₄ alkylamino group (e.g. methylamino, ethylamino, dimethylamino, diethylamino groups), C₁₋₄ alkanoylamino group (e.g. formamide, acetamide group) and so on. In the case where the ring A is pyrrole or pyrrolidine ring, as substituent(s) optionally substituted at N-position, use is made of, besides the above-mentioned C₁₋₄ alkyl group, C₂₋₄ alkenyl group, C₂₋₄ alkynyl group, C₃₋₆ cycloalkyl group, C₁₋₄ alkanoyl group, benzoyl group, substituted benzoyl group, hydroxy C₁₋₄ alkyl group, C₁₋₄ alkoxy-C₁₋₄ alkyl group (especially methoxyethyl group, ethoxyethyl group), phenyl group, substituted phenyl groups (e.g. halogenophenyl such as p-chlorophenyl, p-methoxyphenyl, 3,4,5-trimethoxyphenyl, or mono-, di- or tri-C₁₋₄ alkoxyphenyl), benzyl group, substituted benzyl group (e.g. halogenobenzyl such as p-chlorobenzyl, C₁₋₄ alkoxy benzyl such as p-methoxybenzyl, diphenylmethyl group) and so on.

The bonding between the ring A and Z may take place at any feasible positions, and, in the case where the ring 25 A is pyrrole or pyrrolidine ring, the bonding may take place at N-position.

B stands for an optionally substituted divalent 5- or 6-membered homocyclic or heterocyclic group. As the homocyclic groups represented by B, use is made of, for example, a divalent 5- or 6-membered hydrocarbon group. As such hydrocarbon group, use is often made of a 5- or 6-membered aliphatic hydrocarbon group (e.g. cyclopentylene, cyclohexylene, 1,3- or 3,5-cyclopentadien-1,3-ylene, cyclopenten-(1,3-, 1,4- or 3,5-)ylene, cyclopentan-1,3-ylene, phenyl-(1,3- or 1,4-)ylene, cyclohexan-(1,3- or 1,4-)ylene, cyclohexen-(1,3-, 1,4-, 1,4-, 3,5- or 3,6-)ylene, 1,3-cyclohexadien-(1,3-, 1,4-, 1,5-, 2,4-, 2,5- or 2,6-)ylene, 1,4-cyclohexadien-(1,3-, 1,4- or 1,5-)ylene,) or phenylene (1,2-phenylene, 1,3-phenylene, 1,4-phenylene), especially 1,4-phenylene. As the heterocyclic groups represented by B, use is made of a divalent 5- or 6-membered heterocyclic group containing one to three hetero-atoms (e.g. N, O, S), having bonding hands at positions which are not adjacent to each other in the ring. As the said 5-membered heterocyclic group represented by B, use is made of, for example, thiophen-(2,4-, 2,5- or 3,4-)ylene, furan(2,4-, 2,5- or 3,4-)ylene, pyrrole-(1,3-, 2,4-, 2,5- or 3,4-)ylene, thiazol-(2,4- or 2,5-)ylene, imidazole(1,4-, 2,4- or 2,5-)ylene, thiadiazol-2,5-ylene, their partially reduced forms (multiple bond being partially reduced) or completely reduced forms (multiple bond being completely reduced). Examples of the said 6-membered heterocyclic ring include, pyridin-(2,4-, 2,5-, 2,6- or 3,5-)ylene, pyran-(2,4-, 2,5-, 2,6-, 3,5-, 3,6- or 4,6-)ylene, pyrazin-(2,5- or 2,6-)ylene, pyrimidin-(2,4- or 2,5-)ylene, pyridazin-3,5-ylene, or their partially reduced forms or completely reduced forms. As especially preferable examples of B include a phenyl-1,4-ylene, thiophen-2,5-ylene, thiazol-2,5-ylene, pyridin-2,5-ylene and so on. The divalent 5- or 6-membered homo or heterocyclic group represented by B may have one or two substituents at its replaceable positions. Examples of the said substituents include a C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl group), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl, propargyl group), C₃₋₈ cycloalkyl group (e.g. cyclopropyl group), halogen atom (e.g. chlorine, bromine, fluorine, iodine) hydroxyl group, C₁₋₄ alkoxy group (e.g. methoxy group), di-C₁₋₄ alkylamino group (e.g. dimethylamino group), halogeno-C₁₋₄ alkyl group (e.g. trifluoromethyl group), oxo group, C₁₋₄ acyl group (e.g. formyl group), and C₁₋₄ alkoxy-C₁₋₄ alkyl group (e.g. methoxymethyl, 2-ethoxyethyl group). The more preferable examples of the said substituents include halogen atom (e.g. chlorine, bromine, fluorine, iodine) and so on.

X stands for an amino, hydroxy or mercapto group. More preferable examples of X include an amino or hydroxy group.

Y stands for a hydrogen atom, halogen atom or group bonded through carbon, nitrogen or sulfur atom.

The halogen atom represented by Y includes fluorine, chlorine, bromine or iodine.

The group represented by Y, which is bonded through carbon, nitrogen or sulfur atom, may be a cyano, carboxyl, carbamoyl, amino, nitro, hydroxyl, mercapto or lower hydrocarbon group, such as a C₁₋₄ alkyl group (e.g. methyl, ethyl propyl, iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl group), C₂₋₄ alkynyl group (ethynyl, 1-propynyl, propargyl group), C₃₋₈ cycloalkyl group (e.g. cyclopropyl group) and so on, C₆₋₁₀ aryl group (e.g. phenyl group, naphthyl group), 5- or 6-membered heterocyclic group containing one to four of hetero-atoms such

as N, S, O (e.g. pyrrolyl, imidazolyl, pyrazolyl, phenyl, furyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, their partially reduced forms or completely reduced forms, dioxolanyl, piperidino, morpholino, N-methylpiperazinyl, N-ethylpiperazinyl, dioxanyl) and so on. In cases where Y is a lower hydrocarbon group, aryl group or 5- or 6-membered heterocyclic group, Y may have one or two substituents. Examples of such substituents include a C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, iso-propyl group), a C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl group), a C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl, propargyl group) or C₃₋₈ (e.g. cyclopropyl group), and, besides, halogen atom (e.g. fluorine), hydroxyl, oxo, a C₁₋₄ alkoxy group (e.g. methoxy group), di-C₁₋₄ alkyl group (e.g. trifluoromethyl group), a C₁₋₄ acyl group (e.g. formyl group), hydroxy-C₁₋₄ alkyl group (e.g. hydroxymethyl, 2-hydroxyethyl group), C₁₋₄ alkoxy-C₁₋₄ alkyl group (e.g. methoxymethyl, 2-ethoxyethyl group) and so on.

The group represented by Y, which is bonded through carbon, nitrogen, oxygen or sulfur atom, may be also (1) an alkoxy group, alkylthio group, alkylcarbonylamino group or alkylcarbonyloxy group, and group specifically described referring to the above-mentioned lower hydrocarbon group is used as the alkyl moiety of these groups, (2) aryloxy group, arylthio group, aroylamino group or aroyloxy group, and phenyl group, naphthyl group or the like is used as the alkyl moiety of these groups, (3) heterocyclic oxy group, heterocyclic thio group, heterocyclic carbonylamino group or heterocyclic carbonyloxy group, and the group shown by the above-mentioned 5- or 6-membered heterocyclic group represented by Y is used as the heterocyclic moiety of these groups or (4) a substituted amino group such as a mono-substituted or di-substituted amino group, and the above-mentioned lower hydrocarbon group, aryl group and 5- or 6-membered heterocyclic group represented by Y are used as the substituted moiety.

The more preferable examples of Y include an amino group and so on.

Z stands for an optionally substituted divalent straight-chained aliphatic group having 5 or less chain-composing atoms, which is optionally bonded through one hetero-atom (nitrogen atom, oxygen atom, sulfur atom or the like) at the site of chain. Examples of the divalent straight-chained aliphatic group having 5 or less chain-composing atoms include a C₁₋₅ alkylene group such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene groups and so on, C₂₋₅ alkenylene group such as vinylene, propenylene, 1- or 2-butenylene, butadienylene, 1- or 2-pentenylene, and 1,3- or 1,4-pentadienylene groups, C₂₋₅ alkynylene group such as ethynylene, 1- or 2-propynylene, 1- or 2-butynylene, 1-, 2- or 3-pentyne groups and so on.

And, as the optionally substituted divalent straight-chained aliphatic group having 5 or less chain-composing atoms, which is optionally bonded through one hetero atom at the site of chain, use is made of a group represented by the formula -Z¹-Z²-Z³-wherein Z¹ and Z³ independently stand for a bond or an optionally substituted divalent C₁₋₄ lower hydrocarbon group (provided that the total number of carbon atoms in Z¹ and Z³ is one to four), and Z² stands for -O-, the formula -S(O)n¹- (wherein n¹ denotes an integer of 0 to 2) or the formula



(R⁴ stands for a hydrogen atom, an optionally substituted lower hydrocarbon group or a C₁₋₄ alkoxy carbonyl group). Examples of the divalent lower hydrocarbon group in the optionally substituted divalent lower hydrocarbon groups represented by Z¹ and Z³ include a C₁₋₄ alkylene group such as methylene, ethylene, trimethylene, tetramethylene and so on, C₂₋₄ alkenylene group such as vinylene, propenylene, 1- or 2-butenylene, butadienylene and so on, C₂₋₄ alkynylene group such as ethynylene, 1- or 2-propynylene, 1- or 2-butynylene and so on, and so on. As the lower hydrocarbon group of the optionally substituted lower hydrocarbon group represented by R⁴, use is made of C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl groups), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl, propargyl groups), C₃₋₈ cycloalkyl group (e.g. cyclopropyl group) and so on. The divalent aliphatic group having straight chained 5 or less chain-composing atoms represented by Z, the divalent lower hydrocarbon groups represented by Z¹ and Z³ and the lower hydrocarbon group represented by R⁴ may have 1 to 2 substituents. Examples of such substituents include, besides a C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, iso-propyl groups), C₂₋₄ alkenyl groups (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl, allenyl groups), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl, propargyl groups), C₃₋₈ cycloalkyl group (e.g. cyclopropyl group) or like this, halogen atom (e.g. fluorine), hydroxyl group, oxo group, C₁₋₄ alkoxy group (e.g. methoxy group), di-C₁₋₄ alkylamino group (e.g. dimethylamino, diethylamino group), halogeno-C₁₋₄ alkyl group (e.g. trifluoromethyl group), C₁₋₄ acyl group (e.g. formyl group), hydroxy-C₁₋₄ alkyl group (e.g. hydroxymethyl, 2-hydroxyethyl group), C₁₋₄ alkoxy-C₁₋₄ alkyl group (e.g. methoxymethyl, 2-ethoxyethyl groups), C₁₋₄ alkoxy-carbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl) and so on.

The C₁₋₄ alkoxy-carbonyl represented by R⁴ include a methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl and so on.

As Z, use is made of, for example C₁₋₅ alkylene (e.g. methylene, ethylene, trimethylene) or a group represented by the formula



10 (Z^{1'} stands for a C₁₋₄ alkylene group, and R^{4'} stands for a hydrogen atom, a C₁₋₄ alkyl group which may be substituted by a C₁₋₄ alkoxy-carbonyl group, formyl group or a C₁₋₄ alkoxy-carbonyl group.). As the C₁₋₄ alkylene represented by Z^{1'}, use is made of, for example methylene, ethylene, trimethylene, tetraethylene and so on, more especially ethylene, trimethylene. As the C₁₋₄ alkyl of the C₁₋₄ alkyl group which may be substituted by a C₁₋₄ alkoxy-carbonyl group, use is made of, for example, methyl, ethyl, n-propyl, n-butyl and so on. As the C₁₋₄ alkoxy-carbonyl, use is made of, for example, methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, n-butoxycarbonyl, tert-butoxycarbonyl and so on. As R^{4'}, use is made of, for example, methyl or tert-butoxycarbonyl.

W represents



25 wherein R stands for a hydrogen atom or optionally substituted C₁₋₄ hydrocarbon group, or may form a 5- to 13-membered cyclic group, taken together with



As the C₁₋₄ hydrocarbon group in the optionally substituted C₁₋₄ hydrocarbon group represented by R, use is made of C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group), C₂₋₄ alkenyl group (e.g. vinyl, allyl, 1-methylvinyl and 2-methylvinyl group) and C₃₋₄ cycloalkyl group (e.g. cyclopropyl and cyclobutyl group). Examples of such substituents include, besides C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl and iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl and allenyl group), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl and propargyl group) or C₃₋₈ cycloalkyl group (e.g. cyclopropyl group), halogen atoms (e.g. fluorine, chlorine, bromine, fluorine, iodine), hydroxyl group, oxo group, C₁₋₄ alkoxy group (e.g. methoxy group), di-C₁₋₄ alkylamino group (e.g. dimethylamino and diethylamino group), halogeno-C₁₋₄ alkyl group (e.g. trifluoromethyl group), C₁₋₄ acyl group (e.g. formyl group), hydroxy-C₁₋₄ alkyl group (e.g. hydroxymethyl, 2-hydroxyethyl group) and C₁₋₄ alkoxy-C₁₋₄ alkyl group (e.g. methoxymethyl, 2-ethoxyethyl group). The number of these substituents is preferable one to three.

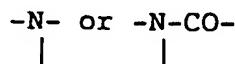
Examples of the 5- to 13-membered heterocyclic group optionally formed by R1 and the adjacent



group include the 5 to 13-membered heterocyclic group being composed of carbon atoms and one to four hetero atoms selected from the group consisting of a nitrogen, oxygen, sulfur atom and so, on. The examples of the 13-membered heterocyclic group include pyrrolyl, imidazolyl, pyrazolyl, piperidino, morpholino, dihydropyridyl, tetrahydropyridyl, N-C₁₋₄ alkylpiperazinyl (e.g. N-methyl piperazinyl, N-methyl piperazinyl group), azacycloheptyl, azacyclooctyl, isoindolyl, indolyl or their partially reduced or completely reduced group, 2-pyrrolidinon-1-yl, 2-piperazinon-1-yl, hexahydro-2-azepinon-1-yl, octahydro-2-oxoindolin-1-yl, 2-oxoindolin-1-yl, 1-oxoisooindolin-2-yl, 2-oxo-1,2,3,42-oxo-1,2,3,4-tetrahydroquinolin-1-yl, 1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl, 1-oxo-5H-benzo-1,2,3,4-tetrahydro-2-azepin-2-yl, 1-oxabenzo-1,2,3,4,5,6-hexahydro-2-azocin-2-yl, 2-oxo-5H-benzo-1,2,3,4-tetrahydro-1-azepin-1-yl, 2-oxobenzo-1,2,3,4,5,6-hexahydro-1-azocin-1-yl, succinimide, glutarimide, 1,4-butanedicarboximide, 1,5-pentanedicarboximide, 1,2-cyclohexanedicarboximide, phthalimide or their partially reduced or completely reduced group. These group may optionally be further cyclized with C₆₋₁₀ aromatic hydrocarbon (e.g. phenyl such as benzene ring, naphthalene ring or

their partially reduced or completely reduced ring) or 5- or 6-membered heterocyclic ring (thiophene, furan, pyrrol, imidazole, pyrazole, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, furazane, pyran, pyridine, pyrazine, pyrimidine, pyridazine or their partially reduced or completely reduced compounds, dioxolan, dioxane, piperidine, morpholine, N-methylpiperazine and N-ethylpiperazine).

- 5 The 5- to 13-membered cyclic group formed by R, R¹ and the adjacent



10

group may optionally have one or two substituents. Examples of such substituents include, besides C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl and iso-propyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl and allenyl group), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl and propargyl group) or C₃₋₈ cycloalkyl group (e.g. cyclopropyl group), halogen atoms (e.g. fluorine, chlorine, bromine, iodine), hydroxyl group, oxo group, C₁₋₄ alkoxy group (e.g. methoxy group), di-C₁₋₄ alkylamino group (e.g. dimethylamino and diethylamino group), halogeno-C₁₋₄ alkyl group (e.g. trifluoromethyl group), C₁₋₄ acyl group (e.g. formyl group), hydroxy-C₁₋₄ alkyl group (e.g. hydroxymethyl, 2-hydroxyethyl group) and C₁₋₄ alkoxy-C₁₋₄ alkyl group (e.g. methoxymethyl, 2-ethoxyethyl group).

As R, use is made of, for example hydrogen atom and so on.

Examples of the cyclic group of the optionally substituted cyclic group represented by R¹ include 5- or 6-membered

- 20 cyclic hydrocarbon group or 5- or 6-membered heterocyclic groups being composed of carbon atoms and one to four hetero-atoms selected from the group consisting of a nitrogen, oxygen and sulfur atom in the ring, or their condensed cyclic group. Examples of the 5-membered cyclic group represented by R¹ include cyclopentadienyl, cyclopentenyl, cyclopentyl, thienyl, furyl, pyrrolyl, thiazolyl, imidazolyl, thiadiazolyl, tetrazolyl or their partially reduced or completely reduced compounds; examples of the 6-membered cyclic group include phenyl, cyclohexyl, cyclohexenyl, cyclohex-25 anienyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl or their partially reduced or completely reduced compounds; and examples of the condensed cyclic group of the 5- or 6-membered cyclic hydrocarbon or heterocyclic group include naphthyl, indenyl, benzothiazolyl, benzoxazolyl, quinolyl, isoquinolyl, quinazolyl or their partially reduced or completely reduced compounds. Especially, as the cyclic groups represented by R¹ phenyl, cyclohexyl, naphthyl, thienyl, cyclopentyl, tetrazolyl or the like are preferable.

- 30 The preferable examples of chain group of the optionally substituted chain group represented by R¹ are C₁₋₄ lower chain-like hydrocarbon group, as exemplified by C₁₋₄ alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group, C₂₋₄ alkenyl group such as vinyl, allyl, 1-methylvinyl and 2-methylvinyl group, and C₃₋₄ cycloalkyl group such as cyclopropyl and cyclobutyl group. The cyclic or chain-like group represented by R¹ may optionally have one or two substituents. Examples of such substituents include C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group), C₂₋₄ alkenyl group (e.g. vinyl, 1-methylvinyl, 1-propenyl, aryl and allenyl group), C₂₋₄ alkynyl group (e.g. ethynyl, 1-propynyl and propargyl group), C₃₋₆ cycloalkyl group (e.g. cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group), C₅₋₆ cycloalkenyl group (e.g. cyclopentenyl and cyclohexenyl group), C₇₋₈ aralkyl group (e.g. benzyl, alphamethylbenzyl and phenetyl group), phenyl group, optionally substituted 5- or 6-membered heterocyclic ring (e.g. tetrazolyl, triazolyl, imidazolyl, oxazolyl, furanyl, thiazolyl, pyridyl, pirazyl 40 triazyl), C₁₋₄ alkoxy group (e.g. methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy group), phenoxy group, C₁₋₄ alkanoyl group (e.g. formyl, acetyl, propionyl, n-butyryl and iso-butyryl group), benzoyl group, C₁₋₄ alkanoyloxy group (e.g. formyloxy, acetyloxy, ethyryloxy propionyloxy, n-butyryloxy and iso-butyryloxy group), benzoyleoxy group, carboxyl group, C₁₋₄ alkoxy-carbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl and tert-butoxycarbonyl group), C₁₋₄ alkoxy-45 carbonyl-C₁₋₄ alkyl (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl, carboxyl-C₁₋₄ alkyl (e.g. carboxylmethyl, carboxylethyl), carbamoyl group, N-substituted carbamoyl group (e.g. N-C₁₋₄ alkyl carbamoyl group such as N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl and N-butylcarbamoyl), N,N-disubstituted carbamoyl group (e.g. 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl and morpholinocarbonyl group, besides N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl and N,N-dibutylcarbamoyl), halogen atoms (e.g. fluorine, chlorine, bromine and iodine), mono-, di- or tri-halogeno-C₁₋₄ alkyl group (e.g. trifluoromethyl group) oxo group, amidino group, imino group, amino group, mono-50 substituted amino group (e.g. mono-C₁₋₄ alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino and butyl amino), di-substituted amino group (e.g. di-C₁₋₄ alkylamino group such as dimethylamino, diethylamino, dipropylamino, diisopropylamino and dibutylamino), 3-to 6-membered cyclic amino group (e.g. aziridinyl, aze-55 tidinyl, pyrrolidinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl and N-ethylpiperazinyl group) alkanoylamido group (e.g. C₁₋₄ alkanoylamido group such as formamide, acetamide, trifluoroacetamide, propionylamido, butyrylamido and isobutyrylamido), benzamido group, carbamoylamino group, N-substituted carbamoylamino group (e.g. N-C₁₋₄ alkyl carbamoylamino group such as N-meth-

ylcarbamoylamino, N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino and N-butylcarbamoylamino), N,N-disubstituted carbamoylamino group (e.g. 1-aziridinylcarbonylamino, 1-azetidinylcarbonylamino, 1-pyrrolidinylcarbonylamino, 1-piperidinylcarbonylamino, N-methylpiperazinylcarbonylamino and morpholinocarbonylamino group, besides N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino and N,N-dibutylcarbamoylamino), C₁₋₃ alkylene dioxy (e.g. methylene dioxy, ethylene dioxy), -B(OH)₂, hydroxyl group, epoxy group (-O-), nitro group, cyano group, mercapto group, sulfo group, sulfino group, phosphono group, dihydroxyboryl group, sulfamoyl group, N-substituted sulfamoyl group (e.g. C₁₋₄ alkyl sulfamoyl group such as N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl and N-butylsulfamoyl), N,N-disubstituted sulfamoyl group (e.g. 1-pyrrolidinylsulfonyl, 1-piperidinylsulfonyl, N-methyl-1-piperazinylsulfonyl and morpholinosulfonyl group, besides di-C₁₋₄ alkyl sulfamoyl group such as N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl and N,N-dibutylsulfamoyl), C₁₋₄ alkylthio group (e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio and tert-butylthio group), phenylthio group, C₁₋₄ alkyl sulfinyl group (e.g. methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl group), phenylsulfinyl group, C₁₋₄ alkyl sulfonyl group (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl and butylsulfonyl group) and phenylsulfonyl group, especially preferable ones being hydroxy group, carboxyl group, sulfo group; phosphono group, dihydroxyboryl group or the like. Among these substituents, those which are capable of being further substituted may have further one or two substituents, as exemplified by C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl group), C₁₋₄ alkoxy group (e.g. methoxy group and ethoxy group), halogen atoms (e.g. fluorine, chlorine, bromine and iodine) and water-soluble group (e.g. hydroxyl group, carboxyl group, sulfo group, phosphono group, amidino group, amino group, methylamino group, ethylamino group, dimethylamino group, diethylamino group, morpholino group, piperidyl group, N-methylpiperazyl group, pyridyl group, trimethylammonium group, triethylammonium group, pyridinium group tetrazolyl group, carboxymethyl group and so on.) Especially, the carboxyl group may be esterified by a C₁₋₄ alkyl group.

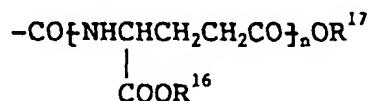
As R¹, use is made of, for example, a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, phenyl, naphthyl and tetrazolyl which may be substituted by the substituent(s) selected from the group consisting of a hydroxy group, carboxyl group, -B(OH)₂, tetrazolyl, methylene dioxy, C₁₋₄ alkyl (e.g. methyl), C₁₋₄ alkoxy (e.g. methoxy), carboxy-C₁₋₄ alkyl (e.g. carboxymethyl), C₁₋₄ alkoxy-carbonyl-C₁₋₄ alkyl (e.g. methoxycarbonylmethyl, ethoxycarbonylmethyl), C₁₋₄ alkanoylamide (e.g. formamide, acetamide), 1-pyrrolidinylcarbonyl group.

COOR² stands for an optionally esterified carboxy group. The COOR² includes one which may be used as intermediate for synthesis, pharmaceutically acceptable one, one which can change to be pharmaceutically acceptable only in body, and so on.

As the optionally esterified carboxyl group represented by COOR², use is especially made of carboxyl group optionally esterified with, for example, a C₁₋₅ alkyl group, an optionally substituted benzyl group or an optionally substituted phenyl group. Examples of the lower alkyl group include methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl, neo-pentyl and tert-pentyl; examples of the optionally substituted benzyl group include benzyl group having one to three substituents of nitro or C₁₋₄ alkoxy such as benzyl, nitrobenzyl and methoxybenzyl; and examples of the optionally substituted phenyl include phenyl group having one to three substituents of nitro or C₁₋₄ alkoxy such as phenyl, nitrophenyl and methoxyphenyl. The more preferable examples of COOR² include a carboxyl group which may be esterified by a C₁₋₅ alkyl, especially methyl, and so on.

P denotes an integer of 1 to 4.

When -W-R¹ denotes a moiety represented by the formula:



wherein COOR¹⁶ and COOR¹⁷ are, independently, an optionally esterified carboxyl group and n denotes an integer of 1 to 5, P denotes 1, 3 or 4. As the optionally esterified carboxyl group represented by COOR¹⁶ and COOR¹⁷, use is made of a carboxyl group which may be esterified by the group selected from the group consisting of a C₁₋₅ alkyl (e.g. methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl, neo-pentyl, tert-pentyl), optionally substituted benzyl preferably such as benzyl which may be substituted by a nitro or C₁₋₄ alkoxy (e.g. benzyl, nitrobenzyl, methoxybenzyl), optionally substituted phenyl preferably such as phenyl which may be substituted by a nitro or C₁₋₄ alkoxy (e.g. phenyl, nitrophenyl, methoxyphenyl) and so on. When P is 2 and W is -CO-NH-, the optionally substituted cyclic group is more preferable as R¹.

Below described is the process for producing the compounds (I) of this invention or their salts.

The compound (I) or its salt can be obtained by acylating a compound (III) or its salt with a compound (II), its salt or reactive derivative at the carboxyl group. The above-mentioned acylating means includes, for example, a procedure of acylating the compound (III) or its salt with the compound (II), its salt or reactive derivative. It is advantageous to

conduct this reaction in the presence of, for example, carbodiimides, diphenylphosphoric azide or diethyl cyanophosphate. The amount of the compound (III) or its salt to be used ranges usually from about 1 to 20 mole equivalents relative to the compound (II) or its salt, reactive derivative at the carboxyl group, preferably about 1 to 5 mole equivalents. The amount of carbodiimides, diphenylphosphoric azide and diethyl cyanophosphate to be used is usually in the range 5 from about 1 to 25 mole equivalents, preferably about 1 to 5 mole equivalents relative to the compound (II) or its salt, reactive derivative at the carboxyl group.

As the carbodiimides, dicyclohexylcarbodiimide is desirable from the stand of practical use, while any other carbodiimides, for example, diphenylcarbodiimide, di-o-tolylcarbodiimide, di-p-tolylcarbodiimide, di-tert-butylcarbodiimide, 10 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide, 1-cyclohexyl-3-(4-diethylaminocyclohexyl)carbodiimide, 1-ethyl-3-(2-diethylaminopropyl)carbodiimide and 1-ethyl-3-(3-diethylaminopropyl)carbodiimide may be used.

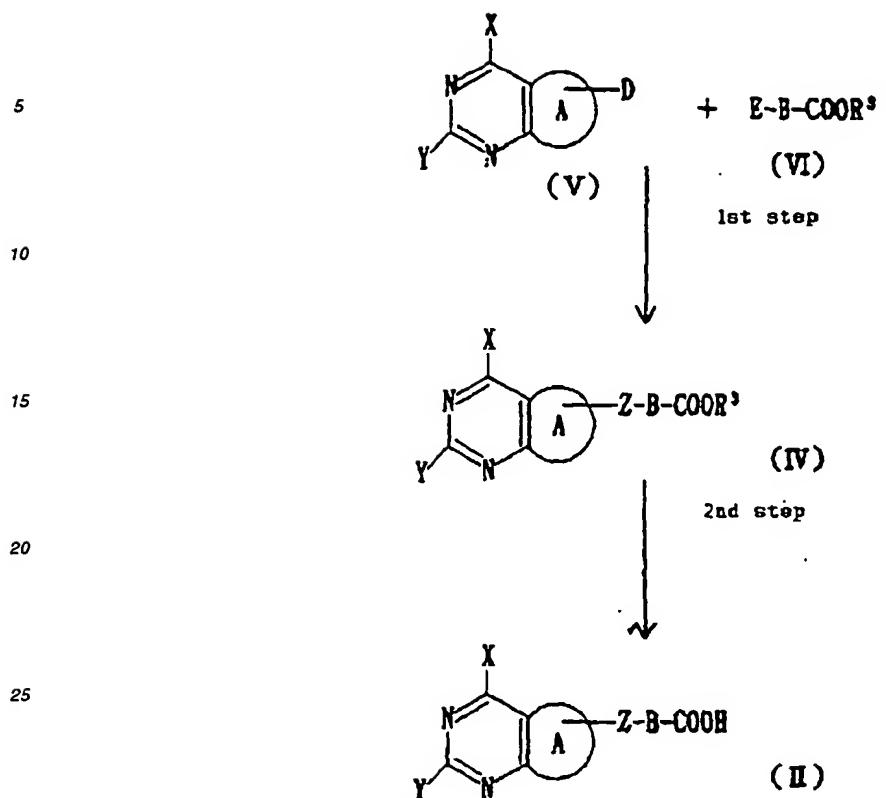
This acylation reaction may be conducted in the presence of an adequate solvent, as exemplified by water, alcohols (e.g. methanol and ethanol), ethers (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme), nitriles (e.g. acetonitrile), esters (e.g. ethyl acetate), halogenated hydrocarbons (e.g. dichloromethane, chloroform and carbon tetrachloride), aromatic hydrocarbons (e.g. benzene, toluene and xylene), acetone, nitromethane, 15 pyridine, dimethyl sulfoxide, dimethylformamide, hexamethylphosphoramide, sulfolane or suitable mixtures of them. This reaction is conducted at a pH usually in the region of about 2 to 14, preferably about 6 to 9, at temperatures usually ranging from about -10°C to the boiling point (up to about 100°C) of the solvent then used, preferably about 0 to 50°C, usually for about 1 to 100 hours. The pH of the reaction solution is, upon necessity, adequately adjusted with, for example, acids (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, nitric acid and acetic acid), bases (e.g. sodium 20 methylate, sodium ethylate, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, barium carbonate, calcium carbonate, sodium hydrogen carbonate, trimethylamine, triethylamine, triethanolamine and pyridine) or buffers (e.g. phosphate buffer, borate buffer and acetate buffer). This reaction can be allowed to proceed more advantageously by the aid of a catalyst capable of accelerating acylation. As such catalysts, use is made of, for example, base catalysts and acid catalysts. Examples of the base catalysts include tertiary amines (e.g. 25 aliphatic tertiary amines such as triethylamine; aromatic tertiary amines such as pyridine, α -, β - or γ -picoline, 2,6-lutidine, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine, dimethylaniline and diethylaniline), while examples of the acid catalysts include Lewis acids [e.g. anhydrous zinc chloride, anhydrous aluminum chloride ($AlCl_3$), anhydrous ferric chloride, titanium tetrachloride ($TiCl_4$), tin tetrachloride ($SnCl_4$), antimony pentachloride, cobalt chloride, cupric chloride and boron trifluoride etherate]. Among the above-exemplified catalysts, 4-dimethylaminopyridine or 4-(1-pyrrolidinyl) 30 pyridine is preferably employed in many cases. The amount of the catalysts to be employed ranges usually from about 0.1 to 10 mole equivalents relative to the compound (II) or its salt, reactive derivative at the carboxyl group, preferably from about 0.1 to 1 mole equivalent. Examples of the reactive derivative of the compound (II) in regard to the carboxyl group include derivative of the compound (II), such as its acid halide (e.g. fluoride, chloride, bromide and iodide), its acid anhydride (e.g. iodoacetic anhydride and isobutyric anhydride), its mixed acid anhydride with lower monoalkyl 35 carbonate (e.g. monomethyl carbonate, monoethyl carbonate, monopropyl carbonate, monoisopropyl carbonate, monobutyl carbonate, monoisobutyl carbonate, mono-sec-butyl carbonate and mono-tert-butyl carbonate), its active esters (e.g. cyanomethyl ester, ethoxycarbonylmethyl ester, methoxymethyl ester, phenyl ester, o-nitrophenyl ester, p-nitrophenyl ester, p-carbomethoxyphenyl ester, p-cyanophenyl ester, phenylthio ester and succinimide ester), its acid azide, its mixed acid anhydride with diester of phosphoric acid (e.g. dimethyl phosphate, diethyl phosphate, dibenzyl 40 phosphate and diphenyl phosphate) and its mixed anhydrides with diester of phosphorous acid (e.g. dimethyl phosphite, diethyl phosphite, dibenzyl phosphite and diphenyl phosphite). In the acylation process using these reactive derivatives, the reaction conditions such as the solvent, catalyst, reaction temperatures and reaction time are substantially the same as those described previously referring to the acylation conducted in the presence of carbodiimide and so on.

Incidentally, in the case of producing the compound or a salt thereof which has a hydroxyl group, amino group, 45 mercapto group or carboxyl group in the compound (I) or its salt, the object compound (I) or its salt can be produced by protecting the hydroxyl group, amino group, mercapto group or carboxyl group of the starting compound with a per se known protective group according to a per se known method (e.g. J. F. W. McOmee, Protective Groups in Organic Chemistry, Plenum Press, London and New York (1973)) followed by subjecting the reaction product to a per se known deprotection reaction.

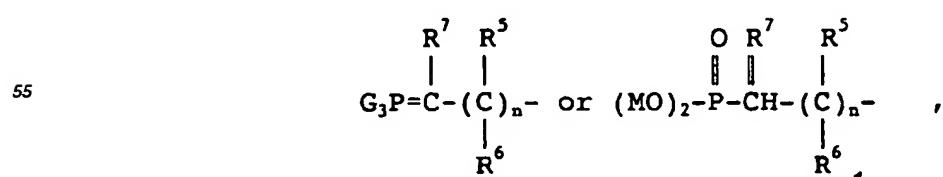
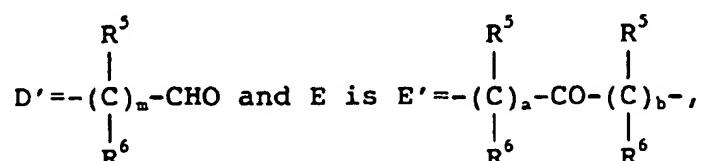
Described in the following is the procedure of producing the starting compound (II), its salt or reactive derivative 50 at the carboxyl group.

The reactive derivative at the carboxyl group of the compound (II) include, among others, acid halide (e.g. acid chloride, acid bromide, etc.), acid anhydride, mixed acid anhydride (e.g. anhydride with methyl carbonate, anhydride with ethyl carbonate, anhydride with isobutyl carbonate, etc.), active ester (e.g. N-hydroxysuccinimide ester, 1-hydroxy-55 benzotriazole ester, N-hydroxy-5-norbornene-2,3-dicarboximide ester, p-nitrophenol ester, 8-oxyquinoline ester, etc.). Among them, acid halide is preferable.

The compound (II), its salt or reactive derivative at the carboxyl group can be produced by, for example, the following reaction steps.



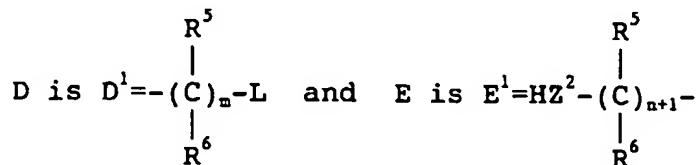
In the above formulae, the ring A, B, D, Y and Z are of the same meaning as defined above, and examples of R³ at the optionally esterified carboxyl group represented by COOR³ include hydrogen atom, or a C₁₋₅ alkyl group, optionally substituted benzyl group or an optionally substituted phenyl group specifically described referring to COOP²; 35 D and E are group being capable of combining with each other to form Z. In the above reaction steps, the covalent bond can be allowed to form between D and E to thereby produce a straight-chain divalent aliphatic group having five or less chain-composing atoms optionally bonded through a hetero-atom at the site of chain. Referring to the synthetic method which permits formation of the covalent bond between the compound (V) or its salt and the compound (VI) or 40 its salt, wherein Z is an optionally substituted divalent aliphatic group having five or less straight-chain atoms, the compound (V) or its salt and the compound (VI) or its salt can be subjected to the so-called reaction causing carbon-carbon bond, followed by subjecting the resultant to reduction, when necessary, to thereby produce the compound (V) or its salt, in case, for example, where D is



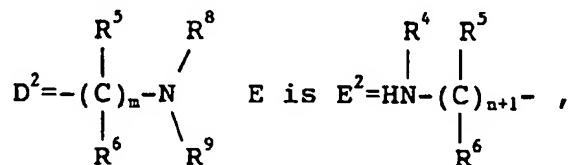
or in the case of vice versa $D=E'$ and $E=D'$.

In the above formulae, a, b, m, n (= a+b) and m+n each denotes an integer in the range of 0 to 3; G stands for phenyl, butyl or cyclohexyl; M stands for ethyl or phenyl; R⁵, R⁶ and R⁷ independently stand for a bond, a hydrogen atom, the divalent lower hydrocarbon group represented by Z¹ and Z² described specifically, or the lower hydrocarbon group represented by R⁴, and they may be different from one another in repeating units m and n.

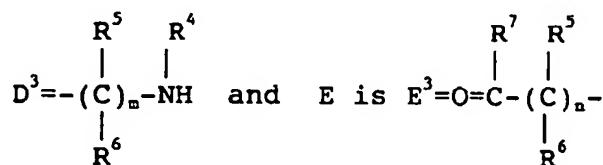
In the case of Z being a group composed of $Z = Z^1 \cdot Z^2 \cdot Z^3$, in the case of, for example,



or in the case of vice versa D=E and E=D', the so-called alkylation reaction is employed, and in the case of, for example, where D is



or in the case of vice versa $D=E^2$, $E=D^2$, so-called amine exchange reaction (glutamine decomposition reaction) is advantageously employed, and in cases where D is



or in the case of vice versa D=E³ and E=D³, a Schiff base or enamine is allowed to form, followed by reduction, when necessary, or subjecting directly to a reductive alkylation reaction.

In the above formulae, m, n, m+n, R⁴, R⁵, R⁶, R⁷ and Z² are of the same meaning as defined hereinbefore; L stands for a leaving group; and R⁸ and R⁹ independently stand for a hydrogen atom or a hydrocarbon group. The leaving group represented by L include, for example, halogen atom (e.g. chlorine, bromine, iodine) or removable group derived easily from hydroxyl group (e.g. methanesulfonyloxy group, benzenesulfonyloxy group, p-toluenesulfonyloxy group and trifluoromethanesulfonyl group). The hydrocarbon group represented by R⁸ and R⁹ may have substituents, and R⁸ and R⁹ may form a cyclic amino group, taken together with adjacent nitrogen atom. Examples of the hydrocarbon group represented by R⁸ and R⁹ include C₁₋₁₈ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tetradecyl, hexadecyl, octadecyl, 1,2-dimethylpropyl, 1-ethylpropyl, 1,2,3-trimethylpropyl, 1-propylbutyl and 2-ethylhexyl group), C₁₋₁₂ alkenyl group (e.g. vinyl, allyl, 1-methylvinyl, 2-methylvinyl, 1-octenyl, 1-decenyl group), C₃₋₁₂ cycloalkyl group (e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantlyl group), C₃₋₈ cycloalkenyl group (e.g. cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclopentadienyl, cyclohexadienyl, cycloheptadienyl, cyclooctadienyl group), C₇₋₁₃ aralkyl group (e.g. benzyl, alpha-methylbenzyl, phenethyl and diphenylmethyl group) and C₆₋₁₀ aryl group (e.g. phenyl, alpha-naphthyl and beta-naphthyl group). Preferred examples of the cyclic amino group which R⁸ and R⁹ cooperate with the adjacent nitrogen atom to form include 4- to 10-membered ring such as azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, pyrazolyl, imidazolinyl, piperidino, morpholino, dihydropyridyl, tetrahydropyridyl, N-methylpiperazinyl, azacycloheptyl, azacyclooctyl, isoindolyl, indolyl, indolinyl, 2-isoindolinyl, azacyclononyl and azacyclodecyl group.

The hydrocarbon group represented by R⁸ and R⁹ and the rings formed by R⁸ and R⁹ in cooperation with the adjacent nitrogen atom may have one or two substituents.

Examples of these substituents include C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl group), C₁₋₄ alkoxy group (e.g. methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy group), C₁₋₄ alkanoyl group (e.g. formyl, acetyl, propionyl, n-butyryl, iso-butyryl group), C₁₋₄ alkanoyloxy group (e.g. formyloxy, acetoxy, propionyloxy, n-butyryloxy, iso-butyryloxy group), carboxyl group, C₂₋₄ alkoxy-carbonyl group (e.g. methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, iso-propoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl group), halogen atom (e.g. fluorine, chlorine, bromine, iodine), hydroxyl group, nitro group, cyano group, trifluoromethyl group, amino group, mono-substituted amino group (e.g. methylamino, ethylamino, propylamino, isopropylamino, butylamino group), di-substituted amino group (e.g. dimethylamino, diethylamino, dipropylamino, diisopropylamino and dibutylamino group), alkanoylamido group (e.g. formamido, acetamido, trifluoroacetamido, propionylamido, butyrylamido, isobutyrylamido group), carbamoyl group, N-substituted carbamoyl group (e.g. N-methylcarbamoyl, N-ethylcarbamoyl, N-propylcarbamoyl, N-isopropylcarbamoyl, N-butylcarbamoyl group), N,N-disubstituted carbamoyl group (e.g. N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl, N,N-dibutylcarbamoyl, 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl, morpholinocarbonyl group), carbamoylamino group, N-substituted carbamoylamino group (e.g. N-methylcarbamoylamino, N-ethylcarbamoylamino, N-propylcarbamoylamino, N-isopropylcarbamoylamino and N-butylcarbamoylamino group), N,N-disubstituted carbamoylamino group (e.g. N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino, N,N-dibutylcarbamoylamino, 1-aziridinylcarbonylamino, 1-azetidinylcarbonylamino, 1-pyrrolidinylcarbonylamino, 1-piperidinylcarbonylamino, N-methylpiperazinylcarbonylamino, morpholinocarbonylamino group), mercapto group, sulfo group, sulfino group, phosphono group, sulfamoyl group, N-substituted sulfamoyl group (e.g. N-methylsulfamoyl, N-ethylsulfamoyl, N-propylsulfamoyl, N-isopropylsulfamoyl, N-butylsulfamoyl group), N,N-disubstituted sulfamoyl group (e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl group (e.g. N,N-dimethylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-diethylsulfamoyl, N,N-dipropylsulfamoyl, N,N-dibutylsulfamoyl, 1-pyrrolidinylsulfonyl, 1-piperidinylsulfonyl, N-methyl-1-piperazinylsulfonyl, morpholinosulfonyl group), C₁₋₄ alkylthio group (e.g. methylthio, ethylthio, propylthio, isopropylthio, n-butylthio, sec-butylthio, tert-butylthio group), C₁₋₄ alkylsulfinyl group (methylsulfinyl, ethylsulfinyl, propylsulfinyl and butylsulfinyl group) and C₁₋₄ alkylsulfonyl group (e.g. methylsulfonyl, ethylsulfonyl, propylsulfonyl, butylsulfonyl group).

Below given is the detailed description of the first step:

For the condensation reaction through the formation of carbon-carbon bonding, is employable according to a known reaction (e.g. aldol reaction, Reformatsky reaction or Wittig reaction), and, as the reduction reaction, catalytic reduction or hydride reduction is usually employed advantageously. In the case of employing aldol reaction for the condensation reaction, as the base catalyst, use is made of, for example, a metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide or barium hydroxide; a metal alkoxide such as sodium methoxide, sodium ethoxide or potassium tert-butoxide; a metal amide such as sodium amide or lithium diisopropylamide; a metal hydride such as sodium hydride or potassium hydride; an organometallic compound such as phenyllithium or butyllithium; and an amine such as triethylamine, pyridine, alpha-, beta- or gamma-picoline, 2,6-lutidine, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine, dimethylaniline or diethylaniline; while as the acid catalyst, use is made of, for example, a mineral acid such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid or boric acid; and an organic acid such as oxalic acid, tartaric acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid or camphorsulfonic acid. Alternatively, the condensation can be conducted by, in accordance with a known method [Ei-Ichi Negishi, Organometallic in Organic Synthesis Vol. 1, John Wiley & Sons, New York, Chichester, Brisbane, Tronto (1980)], deriving a silylenol ether compound from ketone, which is subjected to condensation with aldehyde or its equivalent in the presence of a Lewis acid [e.g. anhydrous zinc chloride, anhydrous aluminum chloride (AlCl₃), anhydrous ferric chloride, titanium tetrachloride (TiCl₄), tin tetrachloride (SnCl₄), antimony pentachloride, cobalt chloride, cupric chloride or boron trifluoride etherate], fluorine anion (e.g. tetrabutyl ammonium fluoride) or trityl perchloride, or by processing the ketone compound with a metal triflate [e.g. dialkyl boron triflate or tin(II) triflate] in the presence of an amine [e.g. triethylamine, pyridine, α-, β- or γ-picoline, 2,6-lutidine, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine, dimethylaniline or diethylaniline] to convert into the enolate, then by subjecting the enolate to condensation with aldehyde or its equivalent. The condensation reaction can be carried out in an appropriate solvent at temperatures ranging from -100°C to the boiling point of the solvent then employed, preferably -78 to 100°C, for a period ranging from one minute to three days. Examples of the reaction solvent include water, liquid ammonia, alcohol (e.g. methanol, ethanol, propanol, iso-propanol, butyl alcohol, sec-butyl alcohol, tert-butyl alcohol, ethylene glycol, methoxyethanol or ethoxyethanol), ether (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme), halogenated hydrocarbon (e.g. dichloromethane, chloroform or carbon tetrachloride), aliphatic hydrocarbon (e.g. pentane, hexane or heptane), aromatic hydrocarbon (e.g. benzene, toluene or xylene), acetonitrile, nitromethane, dimethylformamide, dimethyl sulfoxide, hexamethylphosphoramide, sulfolane or a suitable mixture of them. In the case of resorting to Wittig reaction for the condensation, reagents to be employed are exemplified by a metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide or barium hydroxide; a metal alkoxide such as sodium methoxide, sodium ethoxide or potassium tert-butoxide; a metal amide such as sodium amide or lithium diisopropylamide; a metal hydride

such as sodium hydride or potassium hydride; an organometallic compound such as phenyllithium or butyl lithium; and an amine such as trimethylamine, pyridine, alpha-, beta- or gamma-picoline, 2,6-lutidine, 4-dimethylaminopyridine, 4-(1-pyrrolidinyl)pyridine, dimethylaniline or diethylaniline. The reaction is carried out in an appropriate solvent at temperatures ranging from -20°C to the boiling point of the solvent then used, preferably 0 to 150°C, for a period ranging from one minutes to ten days. As the solvent, use is made of, for example, liquid ammonia, alcohol (e.g. methanol, ethanol, propanol, iso-propanol, butyl alcohol, sec-butyl alcohol, tert-butyl alcohol, ethylene glycol, methoxyethanol or ethoxyethanol), ether (dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme), aliphatic hydrocarbon (e.g. benzene, toluene or xylene), dimethylformamide, dimethyl sulfoxide, hexamethyl phosphoramide, sulfolane or a suitable mixture of them. Furthermore, Reformatskii reaction can be employed for causing the condensation.

Referring to the conditions for Reformatskii reaction, the reagent which is usable includes, for example, zinc, magnesium, aluminum or tin, and the reaction itself can be conducted at temperatures ranging from -20°C to the boiling point of the solvent then used, preferably 0 to 150°C, for a period ranging from 30 minutes to three days. As the solvent, there may be used, for example, ether (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme) aliphatic hydrocarbon (e.g. pentane, hexane or heptane), aromatic hydrocarbon (e.g. benzene, toluene or xylene) or a suitable mixture of them.

The alkylation type reaction or amine exchange type reaction is conducted by allowing a compound (V) or its salt and a compound (VI) or its salt to undergo reaction, as such or in an appropriate reaction solvent, at temperatures ranging from about -10°C to the boiling point of the solvent then employed, preferably about 10 to 80°C, for a period ranging from about ten minutes to 48 hours. The ratio of the compound (VI) or its salt to be used ranges from 1 to 50 moles relative to 1 mol of the compound (V) or its salt, more preferably about 1 to 10 moles. The reaction solvent is exemplified by water, alcohol (e.g. methanol, ethanol, propanol, iso-propanol, butyl alcohol, sec-butyl alcohol, tert-butyl alcohol, ethylene glycol, methoxyethanol or ethoxyethanol), ether (e.g. diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme), halogenated hydrocarbon (e.g. dichloromethane, chloroform or carbon tetrachloride), nitrile (e.g. acetonitrile), aliphatic hydrocarbon (e.g. pentane, hexane, heptane or octane), cyclic aliphatic hydrocarbon (e.g. cyclopentane or cyclohexane), aromatic hydrocarbon (e.g. benzene, toluene or xylene), nitromethane, pyridine, dimethylformamide, dimethyl sulfoxide, hexamethyl phosphoramide, sulfolane or a suitable mixture of them. And, it is, in some instances, desirable to carry out the reaction in the presence of a base, when necessary. Furthermore, when a phase-transfer catalyst (e.g. cetyl trimethylammonium chloride) is used in an amount of 0.01 to 0.2 equivalent, preferably about 0.02 to 0.05 equivalent, relative to the compound (V) or its salt, or the compound (VI) or its salt, the reaction can be allowed to proceed advantageously as well. In the case of the amine exchange type reaction, the reaction can in some instances be allowed to proceed under milder conditions, when a compound (V) or its salt is converted into a quaternary salt, such as the salt with methyl bromide, methyl iodide, methyl methanesulfonate, methyl benzenesulfonate or methyl p-toluenesulfonate. The above-mentioned reaction causing a Schiff base to be formed is conducted by allowing a compound (V) or its salt and a compound (VI) or its salt, as such or in an appropriate solvent, to undergo reaction at a molar ratio of (V)/(VI) = about 10 to 0.1 at temperatures ranging from -10°C to the boiling point of the solvent then used, preferably 0 to 50°C, for a period of time in the region of about ten minutes to 48 hours. In this reaction, the compound (V) or its salt and (VI) or its salt, after having their aldehyde or ketone moieties protected in the form of acetal or ketal, may be used as well. As the reaction solvent, a non-aqueous one is preferable, which is exemplified by alcohol (e.g. methanol, ethanol, propanol, iso-propanol, butyl alcohol, sec-butyl alcohol, tert-butyl alcohol, ethylene glycol, methoxyethanol or ethoxyethanol) ether (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme), ester (e.g. methyl acetate or ethyl acetate), halogenated hydrocarbon (e.g. dichloromethane, chloroform or carbon tetrachloride), nitrile (e.g. acetonitrile), aliphatic hydrocarbon (e.g. pentane, hexane, heptane or octane), cyclic aliphatic hydrocarbon (e.g. cyclopentane or cyclohexane), aromatic hydrocarbon (e.g. benzene, toluene or xylene), acetone, nitromethane, pyridine, dimethylformamide, dimethyl sulfoxide, hexamethyl phosphoramide, sulfolane or a suitable mixture of them. As a dehydrating agent, for example, molecular sieves, calcium chloride, magnesium sulfate, sodium sulfate or calcium sulfate is added, or the pH value of the reaction mixture is adequately adjusted with an acid (e.g. hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid or phosphoric acid), a base (e.g. a metal hydroxide such as sodium hydroxide, potassium hydroxide, lithium hydroxide or barium hydroxide; sodium methoxide, sodium ethoxide, potassium tert-butoxide, sodium carbonate, potassium carbonate, barium carbonate, calcium carbonate, sodium hydrogencarbonate, trimethylamine, triethylamine, triethanolamine or pyridine) or a buffer solution (e.g. phosphate buffer, borate buffer or acetate buffer) to thereby enhance and improve the reaction rate and yields. The reduction and reductive alkylation of the Schiff base are carried out through hydride reduction or catalytic reduction in an appropriate solvent at temperatures ranging from about -40°C to the boiling point of the solvent then employed, more preferably about 0 to 50°C. As the solvent employable, mention is made of, besides the solvents usable in the alkylation type reaction or amine exchange type reaction as described previously, acetic acid ester (e.g. methyl acetate or ethyl acetate). The catalytic reduction is carried out by using an adequate solvent at temperatures ranging from about -40°C to the boiling point of the solvent, more preferably about 0 to 50°C. As the solvent, use is made of, for example, water, alcohol (e.g. methanol, ethanol, propanol, iso-propanol, butyl alcohol, sec-butyl alcohol,

5 tert-butyl alcohol, ethylene glycol, methoxyethanol or ethoxyethanol), acetic acid ester (e.g. methyl acetate or ethyl acetate), ether (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme or diglyme), aromatic hydrocarbon (e.g. benzene, toluene or xylene), pyridine, dimethylformamide or a suitable mixture of them. As the catalyst for catalytic reduction, use is made of, for example, palladium, platinum, rhodium or Raney nickel. In this case, the reaction can, in some instances, be allowed to proceed advantageously by adding a small amount of acetic acid, trifluoracetic acid, hydrochloric acid or sulfuric acid. Examples of the reagent in the hydride reduction include lithium aluminum hydride, sodium borohydride, lithium borohydride or sodium cyanoborohydride, and the amount of the reagent to be employed ranges from about equimole to 100-fold moles, usually 2-fold to 20-fold the molar quantity.

10 And, when the ring A is furan, thiophene, thiophen-1-oxide, thiophene-1,1-dioxide or N-substitutedpyrrole ring and -Z²- is -NH-, the said group -NH-, in some instances, undergoes ring-closure with the ring A to form a tricyclic compound (e.g. pyrrolo[3',2':4,5]pyrrolo[2,3-d]pyrimidine derivative). In this case, the tricyclic compound can be easily converted to the object dicyclic compound by processing with an acid or a base.

15 Second Step:

20 The compound (IV) or its salt as obtained in the first step can be converted into the compound (II) or its salt by allowing its ester residual group [-COOR³] to undergo the per se known deprotection reaction as employed in the production of the compound (I) or its salt.

25 And, the starting compound (II) or its salt can be produced also by the reaction steps as shown in the following.

25

30

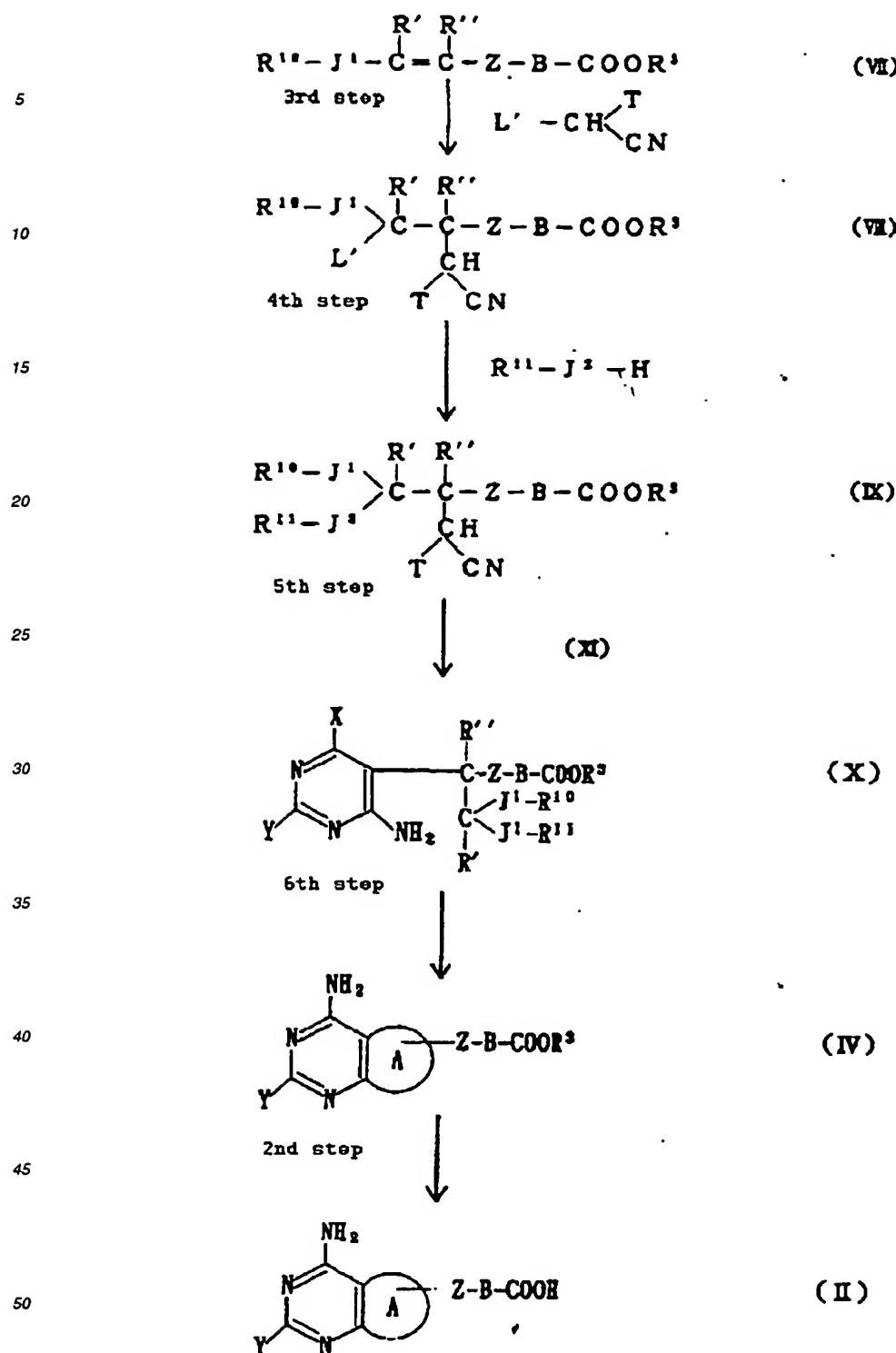
35

40

45

50

55



In the above reaction steps, the ring A, B, R³, X, Y and Z are of the same meaning as defined above; J¹ and J² independently stand for oxygen or sulfur; R¹⁰ and R¹¹ independently stand for a hydrocarbon group; L' stands for a halogen atom (e.g. chlorine, bromine or iodine); T stands for a cyano group or a group represented by -COOR¹², -CSOR¹² or -CSSR¹² [wherein R¹² stands for a hydrocarbon residual group]; R' and R'' independently stand for hydrogen atom or a C₁₋₃ alkyl group, a C₂₋₃ alkenyl group, a C₂₋₃ alkynyl group or a cyclopropyl group as described in

detail as the substituents on the ring A. Examples of the hydrocarbon residue represented by R¹⁰, R¹¹ and R¹² include C₁₋₅ lower alkyl group (e.g. methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl, sec-pentyl, neo-pentyl and tert-pentyl group). These lower alkyl, benzyl and phenyl group may have one to three substituents. Such substituents include, for example, halogen atom (e.g. fluorine, chlorine, bromine, iodine), nitro group, cyano group, alkoxy group having about one to four carbon atoms (e.g. methoxy, ethoxy, propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy group), C₁₋₄ alkyl group (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl group), alkanoyl group of about one to four carbon atom (e.g. formyl, acetyl, propionyl, n-butyryl, iso-butyryl group), trifluoromethyl group and so on.

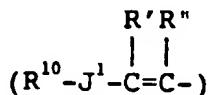
Given below is detailed description on the above reaction steps:

10

Third Step:

This is a step of producing the compound (VIII) or its salt by subjecting the double bond

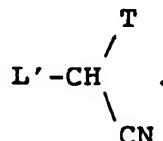
15



20

of the compound (VII) or its salt to addition reaction to

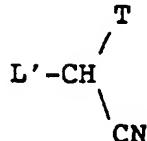
25



30

The amount of

35



40

relative to the starting compound (VII) or its salt. The amount to be used ranges generally from about 0.5 to 4 mole equivalents, preferably about 0.8 to 1.5 mole equivalents. This reaction can be carried out in an adequate solvent at temperatures ranging from about - 10°C to the boiling point of the solvent (up to about 100°C), preferably about 0 to 50°C, for about 30 minutes to 48 hours. Examples of the solvent include alcohol (e.g. methanol and ethanol), ether (e.g. dimethyl ether, diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme), nitrile (e.g. acetonitrile), ester (e.g. ethyl acetate), halogenated hydrocarbon (e.g. dichloromethane, chloroform and carbon tetrachloride), aromatic hydrocarbon (e.g. benzene, toluene and xylene) or a suitable mixture of them. In conducting the reaction, irradiation of light or addition of an organic peroxide can, in some instances, permit the reaction to proceed more advantageously. Examples of the organic peroxide include t-butyl hydroperoxide, peracetic acid, perbenzoic acid and m-chloroperbenzoic acid. The compound (VIII) or its salt as obtained by the above procedure is of relatively high reactivity and may be isolated in this stage, while it can also be used directly in the following step without being isolated.

Fourth step:

55

The compound (VIII) or its salt as obtained in the third step can be led to the compound (IX) or its salt by allowing the former to react with alcohol or thiol represented by R¹¹-J²-H in an appropriate solvent at temperatures ranging from about -10°C to the boiling point (up to about 100°C) of the solvent then employed, preferably about 0 to 50°C, for about 10 minutes to 24 hours. Examples of the solvent to be employed include ether (e.g. dimethyl ether, diethyl ether,

tetrahydrofuran, dioxane, monoglyme or diglyme), nitrile (e.g. acetonitrile), ester (e.g. ethyl acetate), halogenated hydrocarbon (e.g. dichloromethane, chloroform or carbon tetrachloride), aromatic hydrocarbon (e.g. benzene, toluene or xylene) or a suitable mixture of them. Incidentally, the alcohol or thiol represented by R¹¹-J²-H may be used in excess to utilize for the solvent as well.

5

Fifth step:

The compound (IX) or its salt, upon reaction with a compound represented by the formula

10



15

[wherein Y is of the same meaning as defined above] or a salt thereof, is led to the compound (X) or its salt by the reaction through the cyano, ester or thioester group to cause cyclization to form the pyrimidine ring.

20

The acid salt of the compound (XI) or its salt includes, for example, salts with a mineral acid such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid, nitric acid, phosphoric acid or boric acid, and with an organic acid such as oxalic acid, tartaric acid, lactic acid, citric acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid or camphorsulfonic acid, while the base salt of the compound (XI-1 : Y= hydroxyl or mercapto group) include, for example, salts formed with sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethyl ammonium, triethyl ammonium, pyridinium or substituted pyridinium.

25

The reaction for ring-closure can, in some instances, be allowed to proceed advantageously under basic conditions. As the base, use is made of, for example, metal alkoxide such as sodium methoxide, sodium ethoxide or potassium tert-butoxide. Examples of the reaction solvent include methanol, ethanol, propanol, tert-butyl alcohol, dimethyl sulfoxide or hexamethyl phosphoramide. The reaction temperatures range from 0 to 150°C, preferably 20 to 100°C, and the reaction time ranges from one to 48 hours. Examples of the reaction solvent include methanol, ethanol, propanol, tert-butyl alcohol, dimethyl sulfoxide, hexamethyl phosphoramide or a suitable mixture of them.

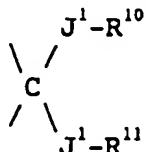
30

Sixth step:

35

When necessary, the group of the formula

40



45

carbonyl group in the compound (X) or its salt is restored to a carbonyl group (>C=O), bringing about spontaneously an intramolecular ring-closure reaction and dehydration reaction to thereby convert the compound (X) or its salt into the compound (IV) or its salt. The restoration reaction to the carbonyl group can be carried out by subjecting the compound (X) or its salt, as such or in a suitable solvent, to a per se known restoration reaction at temperatures ranging from about -10°C to the boiling point (up to about 100°C) of the solvent then employed, preferably about 0 to 50°C for about 10 minutes to 100 hours. The intramolecular ring-closure and dehydration reactions in the step of producing the compound (IV) or its salt normally allow the group X on the pyrimidine ring to condense spontaneously to the carbonyl group (>C=O) in the course of or after restoration to thereby form the ring A. In conducting the the reaction, it is also possible to allow the the reaction to proceed promptly and in an improved yield by permitting an acid catalyst to present in the reaction system. As the acid catalyst, use is made of, for example, mineral acids, organic acids or Lewis acids as described in detail referring to the aldol reaction. Also the carbonyl group

50

(>C=O) can be reduced to a hydroxymethyl group (>CHOH), whose hydroxy moiety is converted into a leaving group L, followed by alkylation reaction with the group X in the same molecule to thereby product the compound (IV) or its salt having the ring A reduced partially. The carbonyl-group reduction, conversion of the hydroxyl group into the leaving group and the intramolecular alkylation are carried out according to per se known procedures. In addition, the compound

- (II) or its salt, or (IV) or its salt can be subjected to a catalytic reduction according to a per se known, procedure to perform partial reduction to thereby convert into the compound (II) or its salt, or the compound (IV) or its salt wherein the ring A is partially reduced. In the case of the compound (II) or its salt whose ring A is pyrrole or pyrrolidine ring, the compound (X) or its salt, or the compound (IV) or its salt can be subjected to a per se known alkylation or acylation reaction to thereby convert into a compound having an N-substituted pyrrole or N-substituted pyrrolidine ring, which falls into the scope of this invention. Furthermore, the compound of this invention whose ring A is an N-substituted pyrrole or N-substituted pyrrolidine ring can be produced also by conducting the above-mentioned alkylation or acylation reaction employing the compound (IV), (II) or its salt whose the ring A is an unsubstituted pyrrole or unsubstituted pyrrolidine ring which is described in Japanese Patent Publication Laid Open No. 167281/1990.
- 5 The starting compound (II) or its salt, whose ring A consists solely of carbon atoms, can be produced by, for example, the reaction steps as shown in the following:
- 10

15

20

25

30

35

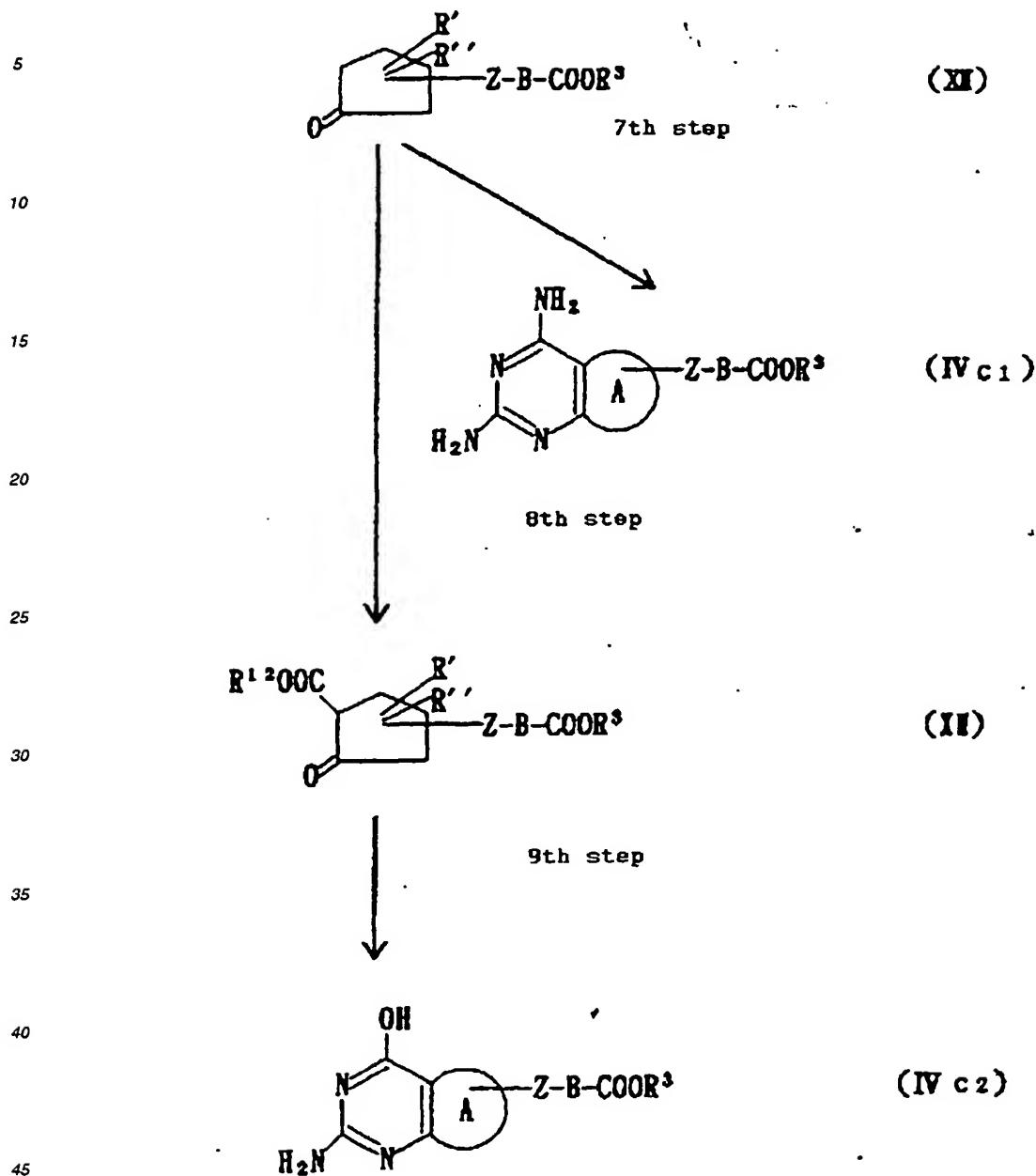
40

45

50

55

[Chemical Formula 21]



50 In the above reaction steps, the ring A, B, R³, R¹², R¹, R["] and Z are of the same meaning as defined hereinbefore, and R¹, R["] and -Z-B-COOR³ are to be understood to form bonding in the consecutive three positions on the cyclopentane ring.

Seventh step:

The compound (XII) or its salt as synthesized by a conventional procedure, upon treatment under heating with dicyandiamide, undergoes cyclization to form a condensed pyrimidine ring, thus yielding the compound (IV_{C1}) or its salt. In this case, the reaction temperatures ranges from 100 to 300°C, more preferably 150 to 250°C, and the suitable

reaction time ranges from one to 24 hours. When required further, dehydrogenation can be effected by following a per se known procedure with a known reagent to introduce an unsaturated bond into the ring A.

Eighth step:

Out of the two alpha-positions adjacent to the carbonyl group in the compound (XII) or its salt, the hydrogen at the alpha-position, which is not substituted with R', R'' or -Z-B-COOR³, is drawn in accordance with a conventional method to cause formation of carbanion, and an ester residue (e.g. carboxyl group which is esterified by a C₁₋₆ alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, tert-butyl, or C₇₋₈ aralkyl such as benzyl) is introduced into the activated position to thereby produce the compound (XIII) or its salt.

Ninth step:

The compound (XIII) or its salt, upon treatment with the compound of the general formula (XI), reacts with its carbonyl group and ester residue to cause ring-closure and cyclization to form a condensed pyrimidine ring anew to thereby produce the compound (IV_{C2}) or its salt. As the reaction conditions, those employed in the fifth step are applied as such. When necessary furthermore, dehydrogenation can be performed in accordance with a per se known method by using a known reagent to introduce an unsaturated bond into the ring A.

The ester derivatives (IV_{C1}), (IV_{C2}) or its salt, as obtained in the 7th and 9th reaction steps, can be converted into respectively corresponding carboxylic acid derivatives by subjecting to deesterification.

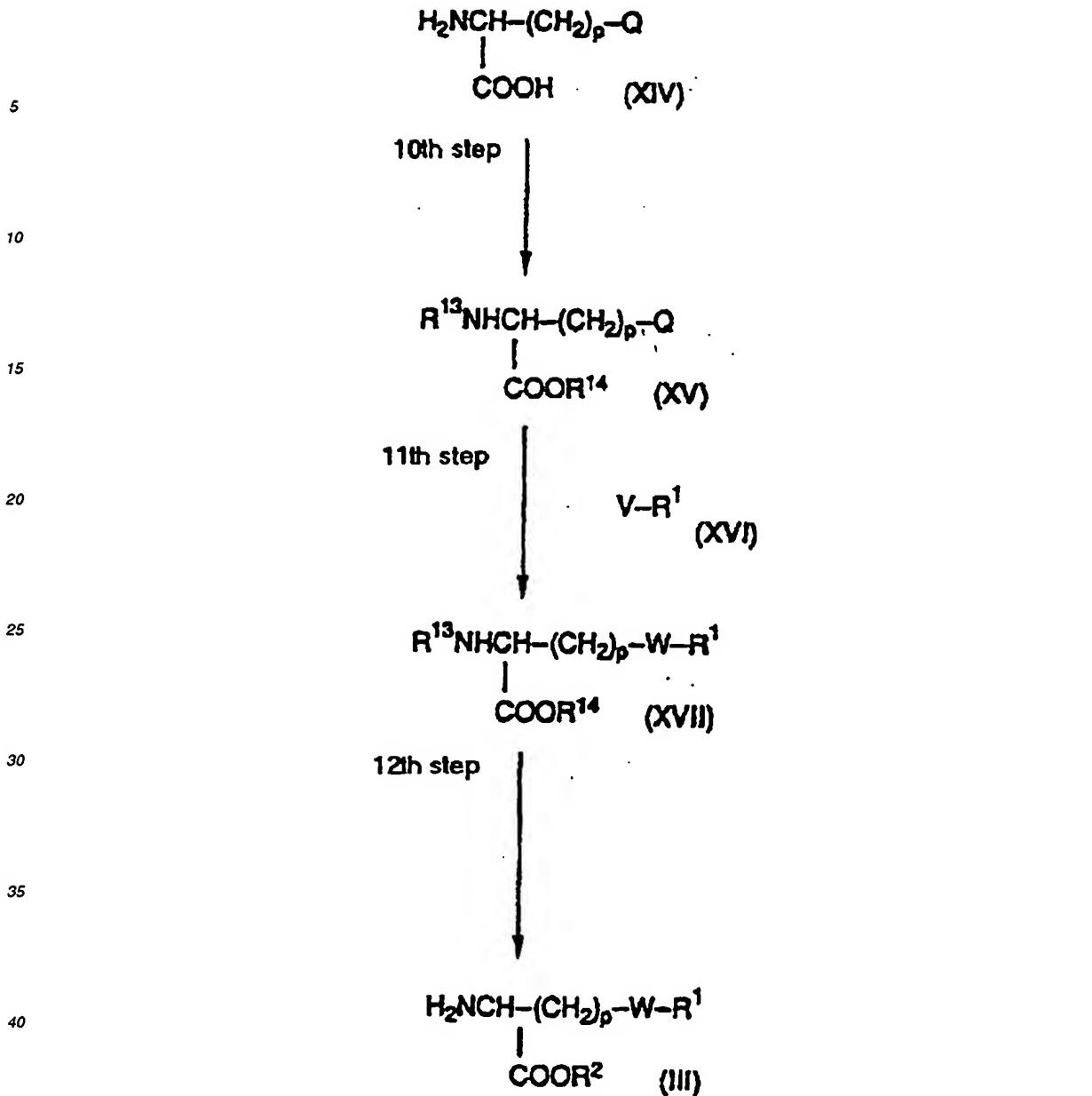
In cases where B is a cycloalkylene group or a substituted phenylene group, such group may be subjected to a catalytic reduction in any suitable one of the first to the ninth steps according to a per se known procedure to thereby convert into corresponding cycloalkylene group.

In cases Y is a hydroxyl, alkoxy, aryloxy, 5- or 6-membered heterocyclic-oxy, mercapto, alkylthio, arylthio, 5- or 6-membered heterocyclic-thio, substituted amino, alkanoylamino, aroylamino or 5- or 6-membered heterocyclic-carbonylamino group, such group may be subjected to a conversion reaction in any suitable one of the second, sixth, seventh and ninth steps according to a per se known procedure to thereby convert into a 5- or 6-membered heterocyclic group, halogen atom, cyano group, carboxyl group, carbamoyl group, nitro group, hydroxyl group, alkoxy group, aryloxy group, 5- or 6-membered heterocyclic-oxy group, mercapto group, alkylthio group, arylthio group, 5- or 6-membered heterocyclic-thio group, substituted amino group, alkanoylamino group, aroylamino group, 5- or 6-membered heterocyclic-carbonylamino group, alkanoyloxy group, aryloxy group or 5- or 6-membered heterocyclic-carbonyloxy group as exemplified by Y.

In cases where the ring A and B contain a sulfur atom or -Z² is -S- (sulfur atom), the compound (I) or its salt of this invention can be converted into the compound wherein the sulfur atom of the ring A, B and -Z²- is changed into S(O)_n [n = 1 or 2] by subjecting the compound (I) or its salt to oxidation directly or in an optional one of the feasible steps. The reaction for oxidation can be carried out in an appropriate solvent, usually in the presence of an oxidizing agent of 0.3 to 3.0 equivalents relative to the compound to be oxidized, preferably 0.5 to 2.5 equivalents at temperatures ranging from -10 to +100°C, preferably 0 to +50°C for 10 minutes to 48 hours, preferably 30 minutes to 24 hours. Preferred examples of the oxidizing agent to be used for the reaction include peracids (e.g. sodium metaperiodate, hydrogen peroxide, peracetic acid, perbenzoic acid and m-chloroperbenzoic acid). Examples of the reaction solvent to be employed include water, acetic acid ketone (e.g. acetone and ethyl methyl ketone), ether (e.g. dimethyl ether, diethyl ether, dioxane, monoglyme and diglyme), halogenated hydrocarbon (e.g. dichloromethane, chloroform and carbon tetrachloride), aliphatic hydrocarbon (e.g. pentane, hexane, heptane and octane), cyclic aliphatic hydrocarbon (e.g. cyclopentane and cyclohexane), aromatic hydrocarbon (e.g. benzene, toluene and xylene), acetonitrile or a suitable mixture of them.

Furthermore, the amino, hydroxyl or mercapto group as represented by X in the compounds (I), (II), (IV) or its salt can be converted into one another, as the case may be, according to a known reaction for substituent replacement on the pyrimidine ring [Supplement volume of "Tampakushitsu/Kakusan/Kouso (Proteins/Nucleic Acids/Enzymes)", Chemical Synthesis of Nucleic Acid, Published by Kyoritsu Publishing Co. of Japan (1968)].

The method of the starting compound (III) or its salt will be described hereinafter. The starting compound (III) or its salt can be produced by, for example, the reaction steps as shown below:



45 In the above reaction scheme, W, R¹, R² and p are of the same meaning as defined hereinbefore, Q and V are group capable of forming the amido-linkage W by bonding to each other. R¹³ stands for amino group and R¹⁴ stands for carboxyl group.

Tenth step:

50 This is the method of producing the compound (IV) or its salt after protecting the amino group and carboxyl group of the alpha-amino acid (VIV) with a per se known protective group. As the protecting group of amino group, use is made of, for example, salts with an acid (e.g. hydrochloride, sulfate, nitrate, phosphate, acetate, trifluoroacetate, p-toluenesulfonate and methanesulfonate), amides (e.g. formyl, acetyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, pivaloyl, benzoyl, p-nitrobenzoyl and p-methoxybenzoyl), imides (e.g. phthaloyl and dithiosuccinoyl), carbamates (e.g. methoxycarbonyl, ethoxycarbonyl, isobutyroxy carbonyl, tert-butoxycarbonyl, cyclohexyloxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl and phenoxy carbonyl), benzyl group (e.g. benzyl, o-nitrobenzyl, diphenyl methyl and trityl) and silyl group (e.g. trimethyl silyl, triethyl silyl, dimethyl-tert-butyl silyl, diphenyl-tert-butyl silyl and diisopropyl-

methyl silyl), while, as the protecting group of carboxylic group, use is made of, for example, esters (e.g. methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, isobutyl, tert-butyl, benzyl, p-nitrobenzyl and phenyl), amides (e.g. N,N-dimethyl amide, pyrrolidinyl amide and piperazinyl amide), silyl esters (e.g. trimethyl silyl, triethyl silyl, dimethyl-tert-butyl silyl, diphenyl-tert-butyl silyl and diisopropylmethyl silyl), metal salts (e.g. sodium, lithium, potassium, calcium, barium, magnesium, copper and silver) and ammonium salts. This reaction can be carried out in an appropriate solvent at temperatures ranging from about 20°C to the boiling point of the solvent, preferably 0 to 80°C, for about 10 minutes to 48 hours. Examples of the solvent to be used for the reaction include water, alcohol (e.g. methanol, ethanol and t-butanol), ether (e.g. diethyl ether, tetrahydrofuran, dioxane, monoglyme and diglyme), nitrile (e.g. acetonitrile), ester (e.g. ethyl acetate), halogenated hydrocarbon (e.g. dichloromethane, chloroform and carbon tetrachloride), aromatic hydrocarbon (e.g. benzene, toluene and xylene), pyridine, dimethylformamide, dimethyl sulfoxide or a mixture of them.

Eleventh step:

For the formation of amido-linkage of W, a known reaction is employed. In the compounds (XV), (XVI) or its salt, when Q is NH₂, V is carboxyl group or its reactive derivative, while, when Q is carboxyl group or its reactive derivative, V is NH₂. The reactive derivatives at the carboxyl group or its reactive derivatives are of the same meaning as those shown by the compound (II) or its salt. Especially, when introduction of the phthaloyl group is intended, it is advantageous to use the Nefken's reagent [Nature, 185, 309, (1960)].

Twelfth step:

The compound (XVII) or its salt obtained by the 11th step can be converted into the compound (III) or its salt by subjecting amino group thereof to a deprotection reaction according to a per se known procedure described in T. W. Green, Protective Group in Organic Synthesis, John Wiley & Sons, New York (1981). In the case where both the amino group and the carboxyl group were protected simultaneously by using the formation of copper chelate, the compound (XVII) or its salt can be converted into the compound (III) or its salt by subjecting the carboxyl group to esterification after removal of the copper by the aid of, for example, hydrogen sulfide, 6N HCl, ethylenediamine tetraacetate (EDTA) under acid conditions.

Incidentally, the reaction for formation of the amido linkage W can be conducted for the compound (XX) or its salt as well.

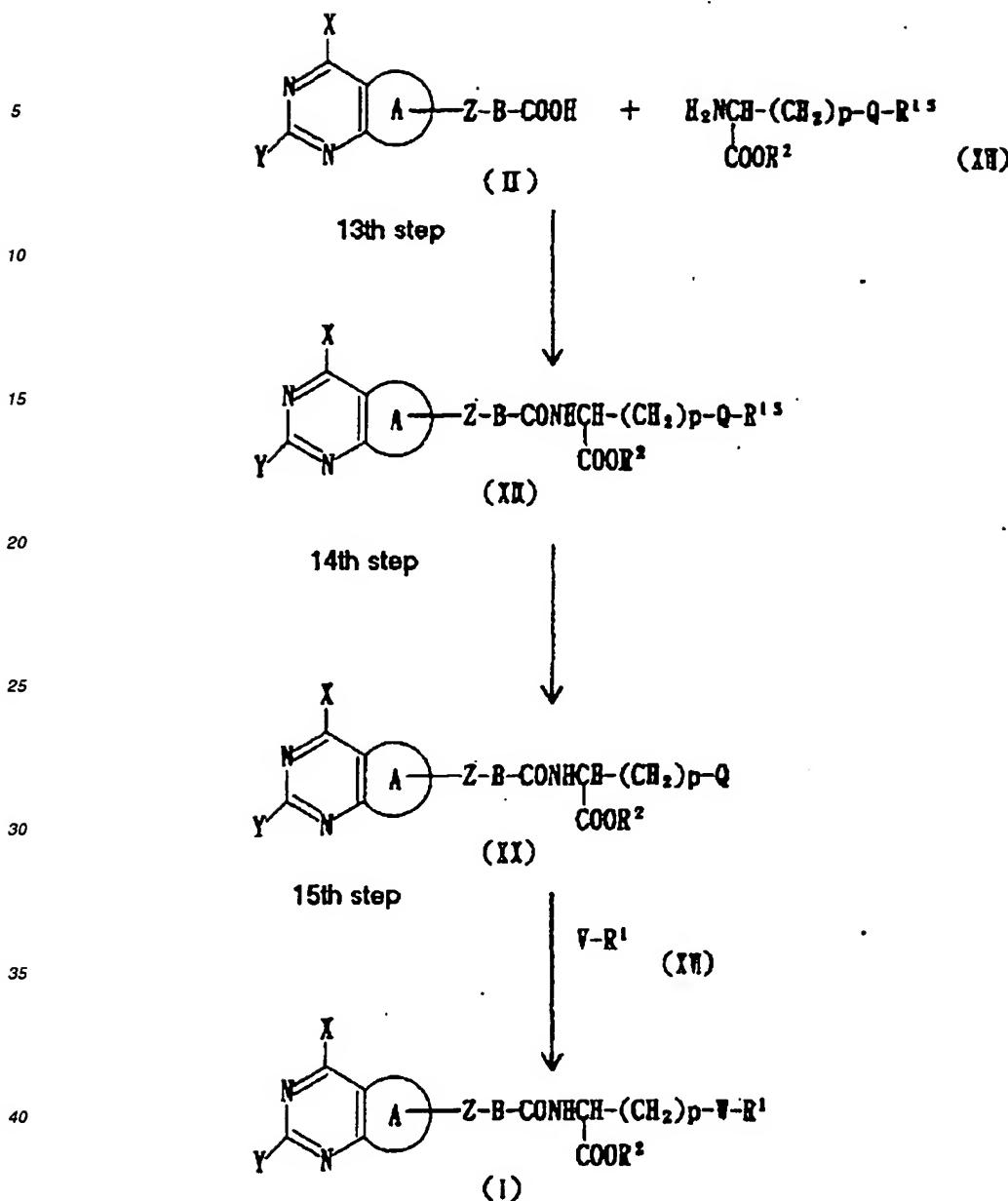
35

40

45

50

55



45 In the above formulae, X, Y, the ring A, Z, B, R¹, p, W, R², Q and V are of the same meaning as defined above.
R¹⁵ is a protecting group of the functional group Q, and, when Q is amino group, R¹⁵ is, for example, carbamate (e.g. methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, tert-butoxycarbonyl, benzylloxycarbonyl or 9-fluorenylmethoxycarbonyl), amido (e.g. chloroacetyl), or silyl group (e.g. trimethylsilyl, triethylsilyl, dimethyl-tert-butylsilyl or diphenyl-tert-butylsilyl); while, when Q is carboxyl group, R¹⁵ is, for example, ester (tert-butyl, benzyl, p-nitrobenzyl or 2-trimethylsilylethyl).
50

Thirteenth step:

The compound (XIX) or its salt can be produced by subjecting the compound (III) or its salt and the compound (XVIII) or its salt to substantially the same condensation as in the case of production of the compound (I) or its salt.

Fourteenth step:

The compound (XIX) or its salt obtained in the 13th step is subjected to the reaction for deprotection of the functional group Q, in substantially the same manner as in twelfth step to thereby produce the compound (XX) or its salt.

5

Fifteenth step:

The compound (XX) or its salt obtained in the 14th step is subjected to a per se known amido-forming reaction to allow the amido-bondage W through Q and V to thereby produce the compound (I) or its salt.

10

Incidentally stating, the reactions, reagents and reaction conditions as well as the protective group as employed upon necessity, which are carried out or employed in the 1st step through 15th step or in the step of producing the starting compound, are conducted by the known methods described in detail in the following literature references. [J. F. M. McMornine, "Protective Groups in Organic Chemistry" Plenum Press, London and New York (1973). [Pine, Hendrickson and Hammond, "Organic Chemistry" (4th edition), [I] to [II], Hirokawa Shoten of Japan] and [M. Fieser and L. Fieser, "Reagent for Organic Synthesis" Vol. 1 to 13, Wiley-Interscience, New York, London, Sydney and Toronto (1969-1988)].

15

Each of the intermediates of the compounds of this invention as well as the compound (I) or its salt of this invention produced by the methods described in the foregoing can be isolated from the reaction mixture by conventional separating means, for example, concentration, solvent extraction, chromatography and recrystallization. The resultant mixed

20

can be used as materials in next step without separating.

25

Examples of salts of the compounds (I), (II), (III), (IV), (IV_{c1}), (IV_{c2}), (V), (VI), (VII), (VIII), (IX), (X), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX) and (XX) obtainable by the above production method include the salts formed with bases such as alkali metals, alkaline earth metals, non-toxic metals, ammonium or substituted ammonium, more specifically, salts with sodium, potassium, lithium, calcium, magnesium, aluminum, zinc, ammonium, trimethylammonium, triethylammonium, triethanolammonium, pyridinium and substituted pyridinium, or salts formed with acids such as mineral acids, such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid and boric acid, and salts formed with organic acids, such as oxalic acid, tartaric acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and camphorsulfonic acid.

30

Incidentally stating, the compounds (V), (VI), (VII), (X), (XI), (XII), (XIV), (XVI), (XVIII) or its salt can be easily produced by conventional methods or per se conventional methods.

Action

The compound (I) or its salt and their salts exhibit inhibitory effect on not less than one kind of the enzymes utilizing folic acid and its related compounds as substrate. Consequently, these compounds can be used in safety and with low toxicity either alone or in combination with any other antitumor agents for the purpose of treatment of chorio-carcinoma, leukemia, breast adenocarcinoma, capital and cervical epithelioma, squamous cell carcinoma, cellule lung cancer and lymphosarcoma that have been treated so far with MTX, as well as other various tumors resistant to MTX. The compound (I) or its salt of this invention perform excellent antitumor effects on, for example, mouse tumor cell strains (e.g. P388, L1210, L5178Y, B16 melanoma, MethA, Lewis Lung Carcinoma, S180 sarcoma, Ehrlich Carcinoma, Colon 26 and 38) and human tumor cell strains (e.g. A549, HL60 and KB), and also have actions of reducing tumors of warm blooded animals (e.g. leukemia, melanoma, sarcoma, mastocytoma and neoplasia) as well as prolonging the life span of cancer-bearing warm blooded animals.

40

Moreover, the compound (I) or its salt of this invention can be used in safety and with lower toxicity as a agent for antirheumatism.

45

Given below is description on the experimental results showing pharmacological effects of the compound (I) or its salt in the present invention.

50

Cell-proliferation inhibitory effects (IC_{50}) of the compound obtained in the first of Example 5 described hereafter against A549 cells were determined by the following method.

55

Each hole of a 96-hole microwell plate was inoculated with 1 ml of human lung cancer A549 cells ($5 \times 10^3/ml$) prepared by a conventional method. The plate was incubated statically for 24 hours at 37°C in 5% CO₂, to which was added a 10% MEM (Nissui Seiyaku, JAPAN) solution of the said compound, and the incubation was continued for further 5 days under the same conditions as above. The culture solution was removed with a micropipette, then 0.1 ml each of a fresh 10% MEM solution (1.0 mg/ml) of MTT (Dojin Kagaku, JAPAN) was added to holes and the plate was incubated at 37°C for 24 hours. Then 0.1 ml each of a 10% SDS (Wako Pure Chemicals Industries, Ltd., JAPAN) was added to holes and the plate was incubated at 37°C for further 24 hours. The absorbance at the wavelength of 590 nm was determined. The concentration of the drug required for decreasing the cell number in the control group by 50% was assumed to be IC_{50} value of the compound. The results were shown in Table 1.

[Table 1]

Test compound	IC ₅₀ (µg/ml)
1st compound of Example 5	0.0012

5

As is apparent from results of the above experiment, the compound (I) or its salt show excellent inhibitory effects against cell proliferation. And, the compound (I) or its salt of this invention or their salts are less toxic and have remarkable anti-tumor activities. Therefore, preparations containing a compound (I) or its salt can be used as antitumor agent aiming at the therapy of tumors of warm-blooded animals, especially mammals (e.g. mouse, rat, cat, dog and rabbit).

10

The compounds (I) or its salt, when intended to use as as an antitumor agent or antirheumatism, can be administered orally or non-orally, as such or after being processed into such dosage forms as powder, granule, tablet, capsule, suppository and injectable solution by means of conventional procedures with use of pharmaceutically acceptable carriers, excipients, diluents and the like. Their dosage amount varies with the species of subject animals, type of diseases, severity of symptoms, kind of compounds or route of administration, and their daily dose for the above warm-blooded animals is about 2.0 to 200 mg/kg body weight, preferably 4.0 to 80 mg/kg body weight in terms of the compound of this invention in the case of oral administration, while the daily dose ranges from about 1.0 to 100, preferably 5-100 mg/kg in the case of non-oral administration. The method of administration for injectable solutions includes, for example, intramuscular injection, intraperitoneal injection, subcutaneous injection and intravenous injection.

15

15

20

25

25

30

35

40

45

The above-mentioned procedures of processing into pharmaceutical preparations are conducted in accordance with *per se* known methods. In manufacturing the above-mentioned oral preparations, for example, tablets, a binder (e.g. hydroxypropyl cellulose, hydroxypropyl methylcellulose or macrogol), a disintegrating agent (e.g. starch and carboxymethylcellulose calcium) and a lubricant (e.g. magnesium stearate and talc), among others, can be suitably incorporated. And, in manufacturing non-oral preparations; for example, injectable solutions, an isotonizing agent (e.g. glucose, D-sorbitol, D-mannitol and sodium chloride), a preservative (e.g. benzyl alcohol, chlorobutanol, methyl p-oxybenzoate and propyl p-oxybenzoate), and a buffer solution (e.g. phosphate buffer and sodium acetate buffer), among others, can be suitably incorporated.

With reference to a specific example of the manufacture of tablets, use is made of, for example, about 1.0 to 50 mg of a compound of this invention, 100 to 500 mg of lactose, about 50 to 100 mg of corn starch and about 5 to 20 mg of hydroxypropyl cellulose, being weighed out for use in the manufacture of one tablet, and they are mixed and tabletted to give a tablet weighing about 100 to 500 mg and measuring about 3 to 10 mm in diameter. And, the resulting tablet can furthermore be processed into an enteric coated tablet by providing coating with use of an about 5 to 10% solution of hydroxypropyl methylcellulose phthalate (about 10 to 20 mg) and castor oil (about 0.5 to 2.0 mg) in acetone-ethanol mixture. Referring to a specific example of producing injectable solutions, for example, about 2.0 to 50 mg per ampoule of sodium salt of the compound (I), (1) is dissolved in about 2 ml of physiological aqueous saline solution, and the solution is filled into an ampoule, followed by fusion and heat sterilization at about 110°C for about 30 minutes, or (2) is dissolved in a solution of about 10 to 40 mg of mannitol or sorbitol in about 2 ml of sterilized distilled water is filled into an ampoule, followed by lyophilization and fusion to thereby prepare an injectable solution. On the occasion of using the lyophilized compound, the said ampoule is opened, and a physiological aqueous saline solution is poured into the ampoule to make a solution having a concentration of, for example 1.0 to 50 mg/ml of the compound. The solution can be used as an injectable preparation subcutaneously, intravenously or intramuscularly.

The present invention is illustrated in further detail by the following Reference Examples and Examples, which are only examples and do not limit the present invention. Modification within the scope of the present invention are permissible.

In the present specification, room temperature means 10-35°C.

45

Reference Example 1

Production of methyl 4-[2-(2-amino-4-hydroxythieno[2,3-d]pyrimidin-5-yl)ethyl]benzoate

50

55

To a solution of 2-amino-4-hydroxy-6-mercaptopurine (144 mg) in dimethylformamide (DMF) was added sodium methylate (1 mmol). To the mixture was added methyl 4-(4-chloro-3-oxobutyl)benzoate (241 mg), then the reaction mixture was stirred for 12 hours at 150°C. The reaction mixture was cooled, then the solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (carrier: 20 g; chloroform:methanol=50:1) to afford the title compound (94 mg; yield 29%).

¹H-NMR(DMSO-d₆) δ: 2.90-3.12(4H,m), 3.84(3H,s), 6.51(2H,s), 6.54(1H,s), 7.37(2H,d,J=8.2Hz), 7.88(2H,d,J=8.2Hz), 10.83(1H,s).

IR(KBr) v: 3460, 3100, 2930, 1720, 1680, 1605, 1490, 1405, 1280, 1180, 1105cm⁻¹.

Reference Example 2

- 5 Production of 4-[2-(2-amino-4-hydroxythieno[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid

To a solution of methyl 4-[2-(2-amino-4-hydroxythieno [2,3-d]pyrimidin-5-yl)ethyl]benzoate (89 mg) obtained in Reference Example 1 in a mixture of tetrahydrofuran (2.7 ml) - water (0.8 ml) was added 1N aqueous solution of sodium hydroxide (1 ml). The mixture was stirred for 20 hours at room temperature. Tetrahydrofuran was distilled off from the reaction mixture, then the residue was neutralized with 1N HCl. Resulting precipitate was collected by filtration, and washed with water, methanol and ether to afford the title compound (69 mg; yield 81%).

1H-NMR(DMSO-d₆) δ: 2.90-3.12(4H,m), 6.54(1H,s), 6.65(2H,s), 7.34(2H,d,J=8.2Hz), 7.86(2H,d,J=8.2Hz), 10.59 (1H,s).

15 IR(KBr) v: 3430, 3120, 2920, 1700, 1670, 1650, 1610, 1480, 1360, 1310, 1280, 1175cm⁻¹.

Reference Example 3

- 20 Production of methyl 4-[2-(2,4-diaminothieno[2,3-d]pyrimidin-5-yl)ethyl]benzoate

In substantially the same manner as in Reference Example 1, the title compound (260 mg, yield 16%) was obtained from 2,4,6-triaminopyrimidine (957 mg) and methyl 4-(4-chloro-3-oxobutyl)benzoate (1.21 g).

25 1H-NMRH(DMSO-d₆) δ: 3.00(2H,t,J=8.0Hz), 3.16(2H,t,J=8.0Hz), 3.84(3H,s), 6.01(2H,s), 6.44(2H,s), 6.49(1H,s), 7.39(2H,d,J=8.2Hz), 7.87(2H,d,J=8.2Hz).

IR(KBr) v: 3450, 3300, 3100, 2950, 1720, 1650, 1635, 1610, 1550, 1505, 1435, 1280, 1180, 1110cm⁻¹.

Reference Example 4

- 30 Production of 4-[2-(2,4-diaminothieno[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid

In substantially the same manner as in Reference Example 2, methyl 4-[2-(2,4-diaminothieno[2,3-d]pyrimidin-5-yl)ethyl]benzoate (240 mg) obtained in Reference Example 3 was subjected to alkali hydrolysis to afford the title compound (201 mg; yield 88%).

35 1H-NMRH(DMSO-d₆) δ: 3.02(2H,t,J=8.0Hz), 3.14(2H,t,J=8.0Hz), 6.07(2H,s), 6.47(2H,s), 6.51(1H,s), 7.35(2H,d, J=8.2Hz), 7.84(2H,d,J=8.2Hz).

IR(KBr) v: 3400, 3340, 3180, 2930, 1660, 1620, 1610, 1560, 1510, 1450, 1375, 1280, 1175, 1100cm⁻¹.

40 Reference Example 5

- Production of methyl 4-[2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl)ethyl]benzoate

To a solution of 2,6-diamino-4-hydroxypyrimidine (631 mg) in dimethylformamide (10 ml) was added methyl 4-(4-chloro-3-oxobutyl)benzoate (1.21 g), and the mixture was stirred for 36 hours at 50°C. The solvent was distilled off under reduced pressure. The residue was purified by column chromatography on silica gel (carrier: 70 g; chloroform: methanol=30:1) to afford the title compound (192 mg; yield 12%).

45 1H-NMR(DMSO-d₆) δ: 2.96(4H,s), 3.84(3H,s), 5.98(2H,s), 6.46(2H,s), 7.05(1H,s), 7.41(2H,d,J=8.2Hz), 7.88(2H,d, J=8.2Hz).

50 IR(KBr) v: 3480, 3410, 3340, 3140, 1715, 1660, 1630, 1610, 1580, 1490, 1460, 1435, 1375, 1310, 1280, 1180, 1110, 1060cm⁻¹.

55 Reference Example 6

- Production of 4-[2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid

In substantially the same manner as in Reference Example 2, methyl 4-[2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl)

ethyl]benzoate (157 mg) obtained in Reference Example 5 was subjected to alkali hydrolysis to afford the title compound (119 mg; yield 80%).

5 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 2.96(4H,s), 6.15(2H,s), 6.64(2H,s), 7.09(1H,s), 7.38(2H,d,J=8.2Hz), 7.86(2H,d,J=8.2Hz).
 IR(KBr) v: 3490, 3420, 3380, 3140, 2930, 1670, 1630, 1610, 1595, 1580, 1460, 1415, 1390, 1315, 1270,
 1170, 1065cm $^{-1}$.

Example 1

10 Production of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo [2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N-(δ)-phthaloyl-L-ornithine methylester

15 To a suspension of 4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoic acid (350 mg) and N(δ)-phthaloyl-L-ornithine methylester hydrochloride (420 mg) in dimethylformamide (DMF) (30 ml) was added dropwise diethyl cyanophosphate (220 mg) under ice-cooling. The mixture was stirred for 10 minutes, to which was added dropwise slowly triethylamine (390 mg), followed by stirring for 4 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by column chromatography on silica gel (carrier: 14 g; chloroform: ethanol containing 1% ammonia=20:1-10:1) to afford the title compound (477 mg; yield 74%).

20 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.70-2.10(6H,m), 2.50-2.75(4H,m), 3.72(2H,m), 3.76(3H,s), 4.60(2H,brs), 4.83(1H,m), 5.10(2H,brs), 6.45(1H,s), 6.91(1H,d,J=8.0Hz), 7.17(2H,d,J=8.0Hz), 7.60-7.85(6H,m), 9.13(1H,brs).
 IR(KBr) v: 3390, 1735, 1710, 1610cm $^{-1}$.

Example 2

25 In substantially the same manner as in Working Example 1, carboxylic acid (II) (1 mmol) was condensed with amino acid (III) (1.1 mmol) in dimethylformamide with the aid of diethyl cyanophosphate to synthesize the following compounds.

30 (1) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-phthaloyl-L-ornithine methylester

35 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.70-2.10(4H,m), 3.01(4H,brs), 3.74(2H,m), 3.78(3H,s), 4.70(2H,brs), 4.88(1H,m), 5.08(2H,brs), 6.41(1H,s), 6.80(1H,d,J=7.0Hz), 7.22(2H,d,J=8.2Hz), 7.65-7.80(4H,m), 7.84(2H,dd,J=5.4, 3.2Hz), 8.25(1H,brs).
 IR(KBr) v: 3370, 1735, 1710, 1610cm $^{-1}$.

(2) N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N(ϵ)-phthaloyl-L-lysine methylester

40 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.20-1.80(4H,m), 1.90-2.10(4H,m), 2.60-2.80(4H,m), 3.70(2H,m), 3.78(3H,s), 4.57(2H,brs), 4.81(1H,m), 4.88(2H,brs), 6.50(1H,s), 6.80(1H,d,J=8.0Hz), 7.27(2H,d,J=8.2Hz), 7.65-7.85(6H,m), 8.25(1H,brs).
 IR(KBr) v: 3370, 2930, 1740, 1710, 1610, 1575, 1400cm $^{-1}$.

45 (3) Methyl 2(s)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]amino-4-phthaloylaminobutyrate

50 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 2.00(2H,m), 2.40(2H,m), 2.65(2H,t,J=7.8Hz), 2.76(2H,t,J=7.2Hz), 3.54(3H,s), 3.87(2H,m), 4.63(2H,brs), 4.85-5.00(3H,m), 6.49(1H,s), 7.27(2H,d,J=8.2Hz), 7.45(1H,d,J=8.2Hz), 7.72(2H,dd,J=5.6, 3.2Hz), 7.85(2H,dd,J=5.6, 3.2Hz), 7.86(2H,d,J=8.2Hz), 8.54(1H,brs).
 IR(KBr) v: 3380, 2970, 1740, 1710, 1610, 1570, 1540, 1435, 1395, 720cm $^{-1}$.

(4) N(α)-[4-[N-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]-N-methylamino]benzoyl]-N-(δ)-phthaloyl-L-ornithine methylester

55 $^1\text{H-NMR}(\text{CDCl}_3/\text{CD}_3\text{OD})$ δ : 1.70-2.10(4H,m), 2.92(3H,s), 2.95(2H,t,J=7.0Hz), 3.70-3.80(3H,m), 3.78(3H(3H,s), 4.78(1H,m), 6.48(1H,s), 6.72(2H,d,J=8.8Hz), 7.60-7.90(6H,m).
 IR(KBr) v: 3380, 1735, 1710, 1635, 1600cm $^{-1}$.

(5) N(α)-[3-chloro-4-[3-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)propyl]benzoyl]-N(δ)-L-ornithine methylester

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.70-2.10(6H,m), 2.50-2.75(4H,m), 3.73(2H,m), 3.78(3H,s), 4.62(2H,brs), 4.85(1H,m), 5.11
 (2H,brs), 6.44(1H,s), 6.91(1H,d,J=8.0Hz), 7.38(1H,d,J=8.0Hz), 7.60-7.90(6H,m), 9.13(1H,
 brs).
 IR(KBr) v: 3380, 1735, 1710, 1610cm $^{-1}$.

10 (6) N(α)-[5-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]-2-thenoyl]-N-(6)-phthaloyl-L-ornithine methyl-
 ester

15 $^1\text{H-NMR}(\text{CDCl}_3/\text{CD}_3\text{OD})$ δ : 1.70-2.10(6H,m), 2.71(2H,m), 2.91(2H,m), 3.73(2H,m), 3.76(3H,s), 4.77(1H,m),
 6.49(1H,s), 6.79(1H,d,J=3.6Hz), 7.45(1H,d,J=8.2Hz), 7.60-7.90(4H,m).
 IR(KBr) v: 3380, 2980, 1735, 1710, 1635, 1610, 1575, 1545, 1380cm $^{-1}$.

20 (7) N(α)-[5-[N-(tert-butoxycarbonyl)-N-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]amino]-2-thenoyl]-N
 (δ)-phthaloyl-L-ornithine methylester

25 $^1\text{H-NMR}(\text{CDCl}_3/\text{CD}_3\text{OD})$ δ : 1.51(9H,s), 1.70-2.10(4H,m), 3.02(2H,t,J=7.8Hz), 3.73(2H,m), 3.76(3H,s), 3.80-
 4.00(2H,m), 4.73(1H,m), 6.53(1H,s), 6.63(1H,d,J=4.2Hz), 7.39(1H,d,J=4.2Hz),
 7.60-7.90(4H,m).
 IR(KBr) v: 3370, 2980, 1735, 1700, 1635, 1610, 1575, 1550, 1395cm $^{-1}$.

30 (8) N(α)-[4-[2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl) ethyl]benzoyl]-N(δ)-phthaloyl-L-ornithine methylester

35 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60-1.90(4H,m), 2.95(4H,brs), 3.60(2H,m), 3.62(3H,s), 4.44(1H,m), 6.08(2H,brs), 6.59
 (2H,brs), 7.07(1H,s), 7.35(2H,d,J=8.2Hz), 7.81(2H,d,J=8.2Hz), 7.85(4H,m), 8.61(1H,d,
 J=7.6Hz).
 IR(KBr) v: 3370, 1740, 1710, 1630, 1570, 1540, 1395cm $^{-1}$.

40 (9) N(α)-[4-[2-(2,4-diaminothieno[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-phthaloyl-L-ornithine. methylester

45 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60-1.90(4H,m), 3.00(2H,m), 3.16(2H,m), 3.60(2H,m), 3.62(3H,s), 4.41(1H,m), 6.05(2H,
 brs), 6.42(2H,brs), 6.50(1H,s), 7.35(2H,d,J=8.2Hz), 7.80(2H,d,J=8.2Hz), 7.84(4H,m),
 8.62(1H,d,J=7.6Hz).
 IR(KBr) v: 3450, 3400, 3320, 1740, 1710, 1640, 1560, 1200cm $^{-1}$.

50 (10) N(α)-[4-[2-(2-amino-4-hydroxy-7H-pyrrolo[2,3-d] pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-phthaloyl-L-ornithine
 methylester

55 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60-1.90(4H,m), 2.80-3.00(4H,m), 3.62(3H,s), 3.63(2H,m), 4.44(1H,m), 5.99(2H,brs),
 6.30(1H,d,J=1.8Hz), 7.27(2H,d,J=8.2Hz), 7.74(2H,d,J=8.2Hz), 7.85(4H,m), 8.61(1H,d,
 J=7.6Hz), 10.13(1H,brs), 10.59(1H,brs).
 IR(KBr) v: 3360, 1740, 1710, 1660, 1630, 1540, 1530, 1395, 710cm $^{-1}$.

60 (11) N(α)-[4-[2-(2-amino-4-hydroxythieno[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-phthaloyl-L-ornithine methyl-
 ester

65 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60-1.90(4H,m), 3.03(2H,m), 3.13(2H,m), 3.62(3H,s), 3.63(2H,m), 4.65(1H,m), 5.90(2H,
 brs), 6.38(1H,s), 7.27(2H,d,J=8.2Hz), 7.74(2H,d,J=8.2Hz), 7.85(4H,m), 8.62(1H,d,
 7.6Hz), 10.76(1H,brs).
 IR(KBr) v: 3450, 3320, 1740, 1710, 1670, 1635, 1600, 1535cm $^{-1}$.

Example 3

70 Production of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)propyl]benzoyl]-N(δ)-(o-
 pyrrolidinocarbonylbenzoyl)-L-ornithine methylester

To a solution of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N(δ)-phthaloyl-L-ornithine

methyleneester (70 mg) in tetrahydrofuran (THF) (1 ml) was added pyrrolidine (20 mg), and the mixture was stirred for 10 hours at room temperature. The solvent was distilled off under reduced pressure, and the residue was purified by means of column chromatography on silica gel (carrier: 8 g; chloroform : ethanol containing 1% ammonia =10:1) to afford the title compound (61 mg, yield 77%).

5 $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 1.60-2.10(10H,m), 2.63(2H,t,J=7.2Hz), 2.73(2H,t,J=7.0Hz), 3.15(2H,t,J=6.4Hz), 3.43(2H,m),
3.58(2H,t,J=6.8Hz), 3.77(3H,s), 4.70(2H,brs), 4.79(1H,m), 4.93(2H,brs), 6.45(1H,s), 7.22(2H,
d,J=8.2Hz), 7.20-7.30(2H,m), 7.40-7.50(3H,m), 7.74(1H,m), 7.81(2H,d,J=8.2Hz), 8.53(1H,brs).
IR(KBr) v: 3330, 1735, 1610, 1570, 1540, 1490, 1450, 1430cm⁻¹

10 Example 4

Production of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)propyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine

15 To a solution of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N(δ)-phthaloyl-L-ornithine methyleneester (70 mg) in a mixture of methanol (1 ml) and tetrahydrofuran (THF) (0.5 ml) was added, under ice-cooling, 1N aqueous solution of sodium hydroxide (1 ml), and the mixture was stirred for three hours at room temperature. The organic solvent was distilled off under reduced pressure. The residue was subjected to filtration with a membrane filter. The filtrate was neutralized with 1N HCl to cause precipitation of crystals. The crystals were collected by filtration, washed with water and dried to afford the title compound (61 mg; yield 87%).

20 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60(2H,m), 1.83(4H,m), 2.50-2.75(4H,m), 3.30(2H,m), 4.37(1H,m), 5.60(2H,brs), 6.21(2H,
brs), 6.47(1H,s), 7.29(2H,d,J=8.2Hz), 7.30-7.55(3H,m), 7.73(1H,dd,J=7.0, 1.8Hz), 7.82(2H,
d,J=8.2Hz), 8.32(1H,m), 8.48(1H,d,J=8.2Hz), 10.54(1H,brs).
25 IR(KBr) v: 3330, 3200, 1660, 1640, 1540cm⁻¹.

Example 5

30 By substantially the same manner as in Working Example 4, methyl ester of carboxylic acid (0.2 mmol) produced in Working Example 2 was subjected to alkali hydrolysis to synthesize the following compounds.

(1) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine

35 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.50-2.00(4H,m), 2.95(4H,m), 3.21(2H,m), 4.40(1H,m), 5.62(2H,brs), 6.26(2H,brs), 6.40
(1H,s), 7.31(2H,d,J=8.2Hz), 7.35-7.55(3H,m), 7.73(1H,dd,J=7.0, 1.8Hz), 7.81(2H,d,
J=8.2Hz), 8.31(1H,t,J=8.2Hz), 8.46(1H,d,J=7.6Hz), 10.50(1H,brs).
IR(KBr) v: 3330, 3200, 2920, 1640, 1545cm⁻¹.

(2) N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N(ϵ)-hemiphthaloyl-L-lysine

40 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.35-1.60(4H,m), 1.70-1.95(4H,m), 2.60-2.80(4H,m), 3.20(2H,m), 4.35(1H,m), 5.50(2H,
brs), 6.08(2H,brs), 6.45(1H,s), 7.27(2H,d,J=8.2Hz), 7.36(1H,m), 7.46(2H,m), 7.73(1H,
dd,J=7.0, 2.6Hz), 7.80(2H,d,J=8.2Hz), 8.34(1H,m), 8.44(1H,d,J=7.6Hz), 10.47(1H,brs).
45 IR(KBr) v: 3330, 3200, 2930, 1640, 1540, 1380cm⁻¹.

(3) N(α)-[4-[N-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]N-methyl]aminobenzoyl]-N(δ)-hemiphthaloyl-L-ornithine

50 $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.50-2.00(4H,m), 2.89(2H,t,J=7.0Hz), 2.92(3H,s), 3.21(2H,m), 3.60(2H,t,J=7.0Hz), 4.40
(1H,m), 5.51(2H,brs), 6.13(2H,brs), 6.43(1H,s), 6.72(2H,d,J=8.8Hz), 7.35-7.55(3H,m),
7.73(1H,m), 7.74(2H,d,J=8.8Hz), 8.31(1H,t,J=8.2Hz), 8.37(1H,d,J=7.6Hz), 10.53(1H,
brs).
IR(KBr) v: 3330, 3200, 2930, 1670, 1640, 1545, 1380, 1200cm⁻¹.

55 (4) N(α)-[3-chloro-4-[3-(2,3-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)propyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine

$^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.60(2H,m), 1.83(4H,m), 2.50-2.75(4H,m), 3.30(2H,m), 4.37(1H,m), 5.63(2H,brs), 6.20

EP 0 530 537 B1

- (2H,brs), 6.46(1H,s), 7.30-7.55(4H,m), 7.70-7.80(2H,m), 7.93(1H,d,J=1.8Hz), 8.32(1H,m), 8.48(1H,d,J=8.2Hz), 10.54(1H,brs).
- IR(KBr) v: 3330, 3200, 1660, 1640, 1540cm⁻¹.
- 5 (5) N(α)-[5-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]-2-thenoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 1H-NMR(DMSO-d₆) δ : 1.60-2.10(6H,m), 2.71(2H,m), 2.85(2H,m), 3.30(2H,m), 4.37(1H,m), 5.57(2H,brs), 6.17(2H,brs), 6.47(1H,s), 6.88(1H,d,J=3.6Hz), 7.30-7.55(3H,m), 7.68(1H,d,J=3.6Hz), 7.75(1H,m), 8.32(1H,m), 8.48(1H,d,J=8.2Hz), 10.49(1H,brs).
- 10 IR(KBr) v: 3340, 3200, 1680, 1660, 1610, 1540, 1455, 1400, 1300cm⁻¹.
- (6) N(α)-[5-[N-(tert-butoxycarbonyl)-N-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]amino]-2-thenoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 15 1H-NMR(DMSO-d₆) δ : 1.04(9H,s), 1.60-2.10(4H,m), 2.95(2H,m), 3.30(2H,m), 4.10(2H,m), 4.30(1H,m), 5.55(2H,brs), 6.15(2H,brs), 6.45(1H,s), 6.72(1H,d,J=4.2Hz), 7.30-7.55(4H,m), 7.75(1H,m), 8.32(1H,m), 8.48(1H,d,J=8.2Hz), 10.53(1H,brs).
- IR(KBr) v: 3370, 3200, 2970, 1695, 1660, 1610, 1580, 1455, 1400, 1300cm⁻¹.
- 20 (7) N(α)-[5-[N-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]amino]-2-thenoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 1H-NMRH(DMSO-d₆/D₂O) δ : 1.60-2.10(4H,m), 2.93(2H,t,J=6.6Hz), 3.24(2H,t,J=6.6Hz), 3.60(2H,m), 4.30(1H,m), 5.85(1H,d,J=4.0Hz), 6.50(1H,s), 7.30-7.55(4H,m), 7.75(1H,m).
- 25 IR(KBr) v: 3340, 2940, 1660, 1610, 1550, 1455, 1400, 1300cm⁻¹.
- (8) N(α)-[4-[2-(2,4-diaminofuro[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 30 1H-NMR(DMSO-d₆) δ : 1.60-1.90(4H,m), 2.95(4H,brs), 3.60(2H,m), 4.40(1H,m), 6.08(2H,brs), 6.57(2H,brs), 7.08(1H,s), 7.35(2H,d,J=8.2Hz), 7.35-7.60(3H,m), 7.75(1H,m), 7.81(2H,d,J=8.2Hz), 8.30(1H,m), 8.61(1H,d,J=7.6Hz).
- IR(KBr) v: 3330, 1630, 1570, 1540, 1395cm⁻¹.
- (9) N(α)-[4-[2-(2,4-diaminothieno[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 35 1H-NMR(DMSO-d₆) δ : 1.60-1.90(4H,m), 3.00(2H,m), 3.15(2H,m), 3.60(2H,m), 3.63(3H,m), 4.41(1H,m), 6.13(2H,brs), 6.52(1H,s), 6.55(2H,brs), 7.35(2H,d,J=8.2Hz), 7.35-7.60(3H,m), 7.75(1H,m), 7.80(2H,d,J=8.2Hz), 8.31(1H,m), 8.62(1H,d,J=7.6Hz).
- 40 IR(KBr) v: 3340, 1630, 1570, 1550cm⁻¹.
- (10) N(α)-[4-[2-(2-amino-4-hydroxy-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 45 1H-NMR(DMSO-d₆) δ : 1.50-2.00(4H,m), 2.85(2H,m), 2.98(2H,m), 3.30(2H,m), 4.37(1H,m), 5.99(2H,brs), 6.29(1H,d,J=1.8Hz), 7.28(2H,d,J=8.2Hz), 7.39(1H,dd,J=6.8, 1.6Hz), 7.40-7.60(2H,m), 7.74(1H,dd,J=7.2, 1.6Hz), 7.79(2H,d,J=8.2Hz), 8.28(1H,t,J=5.4Hz), 8.48(1H,d,J=7.8Hz), 10.13(1H,brs), 10.59(1H,brs).
- IR(KBr) v: 3340, 3200, 1690, 1640cm⁻¹.
- (11) N(α)-[4-[2-(2-amino-4-hydroxythieno[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine
- 50 1H-NMR(DMSO-d₆) δ : 1.50-2.00(4H,m), 2.90-3.10(4H,m), 3.30(2H,m), 4.39(1H,m), 6.53(2H,brs), 6.55(1H,s), 7.32(2H,d,J=8.2Hz), 7.37(1H,dd,J=6.8, 1.6Hz), 7.40-7.60(2H,m), 7.75(1H,dd,J=7.2, 1.6Hz), 7.81(2H,d,J=8.2Hz), 8.30(1H,t,J=5.4Hz), 8.51(1H,d,J=7.8Hz), 10.85(1H,brs).
- 55 IR(KBr) v: 3340, 3200, 1690, 1640, 1540, 1505cm⁻¹.
- (12) 2(s)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl) propyl]benzoylaminopropyl]benzoylaminoo-4-hemiphthaloylaminobutyric acid

⁵ ¹H-NMR(DMSO-d₆) δ: 1.75-2.20(4H,m), 2.70(4H,m), 3.28(2H,m), 4.49(1H,m), 5.84(2H,brs), 6.41(2H,brs), 6.51(1H,s), 7.29(2H,d,J=8.2Hz), 7.30-7.55(3H,m), 7.76(1H,dd,J=7.0, 1.8Hz), 7.81(2H, d,J=8.2Hz), 8.30(1H,m), 8.53(1H,d,J=7.2Hz), 10.68(1H,brs).
IR(KBr) v: 3325, 3200, 2930, 1640, 1545, 1535, 1500, 1380cm⁻¹.

¹⁰ Example 6

Production of methyl N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N-(3-borophenyl)-L-glutamate

¹⁵ To a DMF solution of 4-[3-(2,4-diamino-7H-pyrrolo [2,3-d]pyrimidin-5-yl)propyl]benzoic acid (700 mg) and methyl N-(3-borophenyl)-L-glutamate hydrochloride (720 mg) were added diethyl cyanophosphate (560 ml) and triethylamine (910 mg). The mixture was stirred for 2 hours at room temperature. The reaction mixture was concentrated under reduced pressure, then the concentrate was washed with water, followed by purification by column chromatography on silica gel (carrier : 5 g; chloroform : methanol =10:1) to afford the subject compound (1.03 g; yield 80%).
²⁰ ¹H-NMR (DMSO-d₆) δ : 1.75-2.30(4H,m), 2.46(2H,m), 2.50(2H,m), 2.71(2H,m), 3.67(3H,s), 4.47(1H,m), 5.39(2H,brs), 5.96(2H,brs), 6.43(1H,s), 7.24(1H,t,J=8.2Hz), 7.31(2H,d,J=8.2Hz), 7.69(1H,d,J=7.4Hz), 7.81(1H,s), 7.83(2H,d, J=8.2Hz), 7.98(2H,s), 8.71(1H,d,J=7.4Hz), 9.85(1H,d,J=4.4Hz), 10.41(1H,brs).
IR(KBr) v : 3340, 2950, 1735, 1665, 1645, 1610, 1545, 1430, 1200, 720 cm⁻¹.

²⁵ Example 7

In substantially the same manner as in Example 6, carboxylic acid (1 mmol.) and methyl N-substituted-L-glutamate hydrochloride (1.1 mmol.) were subjected to condensation using diethyl cyanophosphate (1.5 mmol.) in DMF in the presence of triethylamine (4 mmol.) to synthesize the following compounds :

(1) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-borophenyl)-L-glutamate
³⁰ ¹H-NMR(CD₃OD) δ : 2.10-2.45(2H,m), 2.56(2H,m), 3.03(4H,m), 3.75(3H,s), 4.66(1H,dd,J=9.0Hz,5.0Hz), 6.46(1H, s), 7.20-7.30(3H,m), 7.38(1H,m), 7.53(1H,m), 7.73(1H,brs), 7.75(2H,d,J=8.2Hz).

(2) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-ethoxycarbonylphenyl)-L-glutamate

³⁵ ¹H-NMR(DMSO-d₆) δ : 1.32(3H,t,J=7.2Hz), 1.8-2.37(2H,m), 2.46(2H,m), 2.96(4H,m), 3.66(3H,s), 4.30(2H,q, J=7.2Hz), 4.49(1H,m), 5.37(2H,brs), 5.99(2H,brs), 6.35(1H,d,J=2.0Hz), 7.33(2H,d,J=8.2Hz), 7.43(1H,t, J=8.0Hz), 7.62(1H,dt,J=8.0Hz,1.4Hz), 7.81(2H,d,J=8.2Hz), 7.83(1H,dd,J=8.0Hz,1.4Hz), 8.23(1H,t,J=1.4Hz), 8.71(1H,d,J=7.2Hz), 10.16(1H,s), 10.35(1H,d,J=2.0Hz).
IR(KBr) v : 3470, 3380, 3200, 2990, 2960, 2940, 2850, 1720, 1610, 1580, 1555, 1490, 1435, 1370, 1290, 1175, 1105, 1085, 1020, 760, 685, 600, 550 cm⁻¹.

(3) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(4-ethoxycarbonylphenyl)-L-glutamate

⁴⁰ ¹H-NMR(DMSO-d₆) δ : 1.31(3H,t,J=7.0Hz), 1.8-2.35(2H,m), 2.50(2H,t,J=5.6Hz), 2.97(4H,m), 3.66(3H,s), 4.28 (2H,q,J=7.0Hz), 4.48(1H,m), 5.37(2H,brs), 5.99(2H,brs), 6.36(1H,s), 7.34(2H,d,J=8.2Hz), 7.71(2H,d, J=8.8Hz), 7.81(2H,d,J=8.2Hz), 7.90(2H,d,J=8.8Hz), 8.72(1H,d,J=7.6Hz), 10.28(1H,s), 10.37(1H,brs).
IR(KBr) v : 3375, 3180, 2975, 2920, 2850, 1735, 1700, 1605, 1575, 1535, 1500, 1420, 1405, 1365, 1305, 1275, 1250, 1215, 1175, 1105, 1020, 855, 770, 750 cm⁻¹.

(4) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-hydroxyphenyl)-L-glutamate

⁴⁵ ¹H-NMR(DMSO-d₆) δ : 1.8-2.3(2H,m), 2.46(2H,t,J=7.4Hz), 2.98(4H,m), 3.66(3H,s), 4.46(1H,m), 6.42(1H,d, J=6.8Hz), 6.47(2H,brs), 6.53(1H,s), 6.93(1H,d,J=6.8Hz), 7.00(1H,t,J=6.8Hz), 7.10(2H,brs), 7.17(1H,s), 7.34(1H, d,J=8.2Hz), 7.83(2H,d,J=8.2Hz), 8.72(1H,d,J=7.0Hz), 9.35(1H,s), 9.82(1H,s), 11.04(1H,brs).

(5) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(4-hydroxyphenyl)-L-glutamate

⁵⁰ ¹H-NMR(DMSO-d₆) δ : 1.9-2.3(2H,m), 2.41(2H,t,J=7.4Hz), 2.96(4H,m), 3.65(3H,s), 4.46(1H,m), 5.38(2H,brs), 6.00(2H,brs), 6.40(2H,d,J=1.0Hz), 6.69(2H,d,J=8.8Hz), 7.34(2H,d,J=8.8Hz), 7.813(2H,d,J=8.0Hz), 8.72(1H,

d,J=7.8Hz), 9.14(1H,s), 9.67(1H,s), 10.36(1H,s).

IR(KBr) v : 3475, 3380, 3310, 2950, 2925, 2910, 2850, 1740, 1640, 1615, 1585, 1545, 1515, 1500, 1440, 1405, 1380, 1340, 1305, 1255, 1240, 1160, 1105, 1090, 1005, 950, 825, 790, 735, 690, 635, 520 cm⁻¹.

5 (6) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)ethyl]benzoyl]-N-[3-(1H-tetrazol-5-yl) phenyl]-L-glutaminat

10 ¹H-NMR(DMSO-d₆) δ : 1.90-2.35(2H,m), 2.50(2H,m), 2.94(4H,m), 3.65(3H,s), 4.48(1H,m), 5.82(2H,brs), 6.43(1H,s), 6.48(2H,brs), 7.34(2H,d,J=8.0Hz), 7.36(1H,t,J=8.0Hz), 7.66(1H,d,J=8.0Hz), 7.83(2H,d,J=8.0Hz), 8.22(1H,s), 8.74(1H,d,J=7.4Hz), 10.08(1H,s), 10.65(1H,s).

IR(KBr) v : 3400, 3200, 2930, 2850, 1735, 1640, 1610, 1570, 1545, 1500, 1470, 1430, 1415, 1380, 1345, 1315, 1295, 1270, 1210, 1090, 1055, 1030, 800, 755, 690 cm⁻¹.

15 (7) Ethyl N-[N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoylamino]-4(S)-methoxycarbonylbutyryl]-glycinate

¹H-NMR(DMSO-d₆) δ : 1.18(3H,t,J=7.2Hz), 1.8-2.2(2H,m), 2.30(2H,t,J=7.2Hz), 2.96(4H,m), 3.64(3H,s), 3.80(2H,d,J=6.0Hz), 4.07(2H,q,J=7.2Hz), 4.41(1H,m), 5.47(2H,brs), 6.09(2H,brs), 6.37(1H,s), 7.33(2H,d,J=9.5Hz), 7.80(2H,d,J=9.5Hz), 8.32(1H,t,J=6.0Hz), 8.70(1H,d,J=6.6Hz), 10.42(1H,brs).

20 (8) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(2-methoxycarbonylphenyl)-L-glutaminat

¹H-NMR(CDCl₃) δ : 2.38(2H,m), 2.64(2H,m), 2.90(4H,m), 3.75(3H,s), 3.88(3H,s), 4.80(1H,m), 6.38(1H,s), 7.07(2H,d,J=8.0Hz), 7.07(1H,t,J=8.0Hz), 7.50(1H,t,J=8.0Hz), 7.65(2H,d,J=8.0Hz), 7.67(1H,d,J=8.0Hz), 7.97(1H,dd,J=1.2Hz,8.0Hz), 8.62(1H,d,J=7.8Hz), 11.14(1H,brs)

25 IR(KBr) v : 3300, 3200, 2980, 2950, 2670, 2450, 1740, 1680, 1650, 1605, 1590, 1525, 1500, 1445, 1435, 1310, 1295, 1260, 1200, 1175, 1130, 1085, 830, 800, 760, 720 cm⁻¹

(9) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-cyanophenyl)-L-glutaminate

¹H-NMR (CDCl₃ + CD₃OD) δ : 2.05-2.45(2H,m), 2.52(2H,t,J=5.4Hz), 2.99(4H,s), 3.78(3H,s), 4.79(1H,m), 6.44(2H,s), 7.18(2H,d,J=8.4Hz), 7.34(2H,m), 7.69(2H,d,J=8.4Hz), 7.74(1H,m), 7.91(1H,s).

IR(KBr) v : 3380, 2920, 2850, 2230, 1735, 1605, 1545, 1480, 1425, 1320, 1305, 1285, 1255, 1210, 1165, 1090, 1015, 795, 755, 680 cm⁻¹

35 (10) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(4-cyanophenyl)-L-glutaminate

¹H-NMR(DMSO-d₆) δ : 1.9-2.35(2H,m), 2.56(2H,m), 2.96(4H,m), 3.65(3H,s), 4.49(1H,m), 5.36(2H,s), 5.99(2H,s), 6.35(1H,d,J=1.8Hz), 7.33(2H,d,J=8.2Hz), 7.75(4H,s), 7.80(2H,d,J=8.2Hz), 8.70(1H,d,J=7.6Hz), 10.37(2H,s).

IR(KBr) v : 3390, 3200, 2930, 2850, 2230, 1740, 1610, 1580, 1535, 1505, 1330, 1315, 1260, 1220, 1180, 1090, 1020, 990, 840, 800, 760, 550 cm⁻¹

45 (11) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-[4-(1H-tetrazol-5-yl)phenyl]-L-glutaminat

¹H-NMR(DMSO-d₆) δ : 1.4-2.35(2H,m), 2.50(2H,m), 2.97(4H,m), 3.66(3H,s), 5.70(2H,brs), 6.41(1H,s), 7.34(2H,d,J=8.0Hz), 7.71(2H,d,J=8.6Hz), 7.82(2H,d,J=8.0Hz), 7.93(2H,d,J=8.6Hz), 8.73(1H,d,J=8.0Hz), 10.14(1H,s), 10.58(1H,s).

50 IR(KBr) v : 3400, 3300, 2920, 2850, 1735, 1635, 1605, 1535, 1500, 1445, 1420, 1370, 1335, 1300, 1245, 1220, 1170, 1155, 1100, 1060, 1030, 1005, 840, 830, 755, 680cm⁻¹

(12) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-[3-(methoxycarbonylmethyl)phenyl]-L-glutaminat

¹H-NMR(DMSO-d₆) δ : 1.80-2.40(2H,m), 2.47(2H,t,J=7.2Hz), 3.61(3H,s), 3.62(2H,s), 3.65(3H,s), 4.46(1H,m), 5.64(2H,brs), 6.27(2H,s), 6.40(1H,d,J=1.0Hz), 6.91(1H,d,J=7.6Hz), 7.22(1H,d,J=7.6Hz), 7.33(2H,d,J=8.0Hz),

EP 0 530 537 B1

7.46(1H,d,J=7.6Hz), 7.49(1H,s), 7.81(2H,d,J=8.0Hz), 8.69(1H,d,J=7.2Hz), 9.92(1H,s), 10.51(1H,d,J=1.0Hz).
IR(KBr) v : 3350, 3200, 2950, 2850, 1735, 1610, 1570, 1550, 1490, 1435, 1330, 1305, 1260, 1200, 1170,
1090, 1010, 795, 770, 720, 690, 600cm⁻¹

5 (13) Methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol -5-yl)-L-glutaminate

10 $^1\text{H-NMR(DMSO-d}_6)$ δ : 2.00-2.35(2H,m), 2.61(2H,m), 2.96(4H,m), 3.64(3H,s), 4.49(1H,m), 5.60(1H,s), 6.85
IR(KBr) v : 3370, 3200, 2920, 1715, 1640, 1610, 1590, 1540, 1500, 1430, 1200, 1180, 1130, 1035, 720cm⁻¹

Example 8

Production of N(α)-[4-[3-(2,4-diamino-7H-pyrrolo [2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N-(3-borophenyl)-L-glutamine

15 To a methanol/tetrahydrofuran (2:1 ; 15 ml) solution of methyl N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)propyl]benzoyl]-N-(3-borophenyl)-L- glutaminic acid (1 g) was added a 1N aqueous solution (6 ml) of sodium hydroxide (6 ml), and the mixture was stirred for 5 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was dissolved in water, whose pH was adjusted to 4 with 1N hydrochloric acid.
20 Resulting precipitates were collected by filtration, washed with water, then dried under reduced pressure to afford the subject compound (839 mg; yield 86%).

25 $^1\text{H-NMR (DMSO-d}_6)$ δ : 1.84(2H,m), 1.90-2.30(4H,m), 2.45(2H,m), 2.71(4H,m), 4.23(1H,m), 5.71(2H,brs), 6.29
IR(KBr) v : 3320, 3200, 2930, 1660, 1640, 1545, 1490, 1425, 1380, 1340, 705 cm⁻¹.

Example 9

30 In substantially the same manner as in Example 8, the carboxylic acid ester (1 g) produced in Example 7 was subjected to alkali hydrolysis to synthesize the following compounds:

(1) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin -5-yl)ethyl]benzoyl]-N-(3-borophenyl)-L-glutamine
35 $^1\text{H-NMR(DMSO-d}_6)$ δ : 1.90-2.30(4H,m), 2.97(4H,m), 4.41(1H,m), 5.74(2H,brs), 6.41(3H,brs), 7.23(1H,t,J=8.0Hz),
7.33(2H,d,J=8.0Hz), 7.46(1H,d,J=7.2Hz), 7.70(1H,brd,J=8.2Hz), 7.82(1H,brs), 7.82(2H,d,J=8.0Hz), 7.99(2H,brs),
8.57(1H,d,J=7.6Hz), 9.85(1H,s), 10.58(1H,brs).

(2) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin -5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamine
40 $^1\text{H-NMR(DMSO-d}_6)$ δ : 1.9-2.4(2H,m), 2.44(2H,m), 2.96(4H,m), 4.41(1H,m), 5.66(2H,brs), 6.32(2H,brs), 6.40
(1H,s), 7.33(2H,d,J=8.4Hz), 7.39(2H,t,J=7.8Hz), 7.60(1H,dt,J=7.8Hz,1.2Hz), 7.78(1H,dd,J=7.8Hz,1.2Hz),
7.79(2H,d,J=8.4Hz), 8.22(1H,t,J=1.2Hz), 8.55(1H,d,J=7.6Hz), 10.12(1H,s), 10.53(1H,s).
IR(KBr) v : 3350, 3200, 2930, 2850, 1645, 1600, 1545, 1500, 1440, 1385, 1300, 1260, 1190, 1095, 1020, 905,
820, 760 cm⁻¹.

45 (3) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin -5-yl)ethyl]benzoyl]-N-(4-carboxyphenyl)-L-glutamine
1H-NMR(DMSO-d₆) δ : 1.8-2.35(2H,m), 2.50(2H,m), 2.96(4H,m), 4.43(1H,m), 5.70(2H,brs), 6.36(2H,brs), 6.41
(1H,s), 7.33(2H,d,J=8.4Hz), 7.73(2H,d,J=8.8Hz), 7.81(2H,d,J=8.4Hz), 7.87(2H,d,J=8.8Hz), 8.55(1H,d,
J=7.6Hz), 10.25(1H,s), 10.56(1H,brs).
50 IR(KBr) v : 3375, 3200(sh.), 2920, 1640, 1600, 1455, 1405, 1380, 1305, 1255, 1100, 855, 770 cm⁻¹,

(4) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin -5-yl)ethyl]benzoyl]-N-(3-hydroxyphenyl)-L-glutamine
55 $^1\text{H-NMR(DMSO-d}_6)$ δ : 1.8-2.3(2H,m), 2.46(2H,t,J=7.4Hz), 2.99(4H,m), 4.39(1H,m), 5.97(2H,brs), 6.42(1H,d,
J=8.0Hz), 6.46(1H,s), 6.62(2H,brs), 6.92(1H,d,J=8.0Hz), 7.04(1H,t,J=8.0Hz), 7.17(1H,s), 7.34(2H,d,
J=8.2Hz), 7.83(2H,d,J=8.2Hz), 8.57(1H,d,J=7.6Hz), 9.34(1H,s), 9.80(1H,s), 10.73(1H,brs).
IR(KBr) v : 3330, 3200, 2920, 2850, 1640, 1610, 1545, 1495, 1445, 1385, 1340, 1225, 1185, 1155, 1090, 855,
770, 690 cm⁻¹.

(5) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(4-hydroxyphenyl)

5 ¹H-NMR(DMSO-d₆) δ : 1.85-2.30(2H,m), 2.94(2H,t,J=7.2Hz), 2.96(4H,m), 4.39(1H,m), 5.58(2H,brs), 6.21
(2H,brs), 6.38(1H,s), 6.36(2H,d,J=8.8Hz), 7.33(2H,d,J=8.2Hz), 7.34(2H,d,J=8.8Hz), 7.81(2H,d,J=8.2Hz),
8.56(1H,d,J=7.8Hz), 9.14(1H,s), 9.67(1H,s), 10.48(1H,brs).
IR(KBr) ν : 3400, 3340, 3220, 2930, 2855, 1650, 1545, 1515, 1450, 1400, 1340, 1305, 1240, 1170, 1100, 835,
770 cm⁻¹

10 (6) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-[3-(1H-tetrazol-5-yl)phenyl]-L-glutamine
¹H-NMR(DMSO-d₆) δ : 1.8-2.4(2H,m), 2.50(2H,m), 2.96(4H,m), 4.42(1H,m), 6.10(2H,brs), 6.48(1H,s), 6.77(2H,brs),
7.33(2H,d,J=8.0Hz), 7.43(1H,d,J=7.6Hz), 7.67(2H,m), 7.82(2H,d,J=8.0Hz), 8.30(1H,s), 8.58(1H,d,J=7.0Hz), 10.13
(1H,s), 10.81(1H,s). IR(KBr) ν : 3340, 3200, 2925, 2850, 1645, 1570, 1545, 1500, 1455, 1400, 1300, 1280, 1255,
1190, 1090, 800, 760, 745, 690, 630, 590, 550 cm⁻¹.

15 (7) N-[N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-L-γ-glutamyl]glycine

20 ¹H-NMR(DMSO-d₆) δ : 1.80-2.15(2H,m), 2.26(2H,t,J=5.8Hz), 2.96(4H,s), 3.68(1H,d,J=5.6Hz), 3.87(1H,d,
J=5.6Hz), 4.27(1H,m), 5.48(2H,brs), 6.12(2H,brs), 6.38(1H,s), 7.33(2H,d,J=8.2Hz), 7.78(2H,d,J=8.26Hz),
8.11(1H,t,J=5.6Hz), 8.48(1H,d,J=7.2Hz), 10.44(1H,brs).
IR(KBr) ν : 3400, 3170, 2920, 1635, 1540, 1495, 1455, 1385, 1290, 1250, 1230cm⁻¹.

(8) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-N-(2-carboxyphenyl)-L-glutamine

25 ¹H-NMR(DMSO-d₆) δ : 1.9-2.4(2H,m), 2.50(2H,m), 3.00(4H,m), 4.40(1H,m), 6.64(1H,s), 6.67(2H,brs), 7.07
(1H,dt,J=1.2Hz,7.8Hz), 7.23(2H,d,J=8.0Hz), 7.29(2H,s), 7.47(1H,dt,J=1.6Hz,8.6Hz), 7.83(2H,d,J=8.0Hz),
8.04(1H,dd,J=1.6Hz,8.4Hz), 8.52(1H,d,J=8.4Hz), 8.56(1H,d,J=8.4Hz), 11.36(1H,s), 12.03(1H,s).
IR(KBr) ν : 3320, 3200, 2910, 2830, 1655, 1640, 1580, 1520, 1495, 2440, 1370, 1285, 1240, 750cm⁻¹.

(9) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-N-(3-cyanophenyl)-L-glutamine

30 ¹H-NMR(DMSO-d₆) δ : 1.92-2.34(2H,m), 2.5(2H;m), 2.96(4H,m), 4.44(1H,m), 5.66(2H,brs), 6.30(2H,brs), 6.40
(1H,s), 7.33(2H,d,J=8.0Hz), 7.48(2H,m), 7.81(3H,d,J=8.0Hz), 8.08(1H,s), 8.57(1H,d,J=7.0Hz), 10.35(1H,s),
10.54(1H,s).
IR(KBr) ν : 3350, 3200, 2925, 2850, 2225, 1640, 1585, 1545, 1500, 1480, 1450, 1430, 1390, 1330, 1300,
1285, 1255, 1190, 1170, 1095, 1015, 790, 755, 680cm⁻¹.

35 (10) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-N-(4-cyanophenyl)-L-glutamine

40 ¹H-NMR(DMSO-d₆) δ : 1.5-2.45(4H,m), 2.96(4H,m), 4.40(1H,m), 5.54(2H,s), 6.19(2H,brs), 6.38(1H,s), 7.32
(2H,d,J=8.2Hz), 7.75(4H,s), 7.80(2H,d,J=8.2Hz), 8.54(1H,d,J=8.0Hz), 10.39(1H,s), 10.46(1H,s).
IR(KBr) ν : 3410, 2930, 2855, 2230, 1645, 1600, 1535, 1510, 1455, 1410, 1310, 1260, 1175, 1100, 840
555cm⁻¹.

(11) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-N-[4-(1H-tetrazole-5-yl)phenyl]-L-glutamine

45 ¹H-NMR(DMSO-d₆) δ : 1.8-2.35(2H,m), 2.50(2H,m), 2.97(4H,m), 4.43(1H,m), 6.15(2H,brs), 6.47(1H,s), 6.81
(2H,s), 7.33(2H,d,J=8.2Hz), 7.76(2H,d,J=8.7Hz), 7.82(2H,d,J=8.2Hz), 7.95(2H,d,J=8.7Hz), . 8.58(1H,d,
J=8.0Hz), 10.22(1H,s), 10.84(1H,s).
IR(KBr) ν : 3400, 3200, 2930, 2850, 1640, 1570, 1540, 1500, 1450, 1430, 1385, 1335, 1310, 1255, 1185, 1155,
1095, 1075, 1020, 1000, 845, 750, 590 525cm⁻¹.

50 (12) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl-N-[3-(carboxymethyl)phenyl]-L-glutamine

55 ¹H-NMR (DMSO-d₆) δ : 1.90-2.40(2H,m), 2.46(2H,t,J=7.0Hz), 2.96(4H,m), 3.50(2H,s), 4.41(1H,m), 5.47(2H,
brs), 6.11(2H,s), 6.35(1H,d,J=8.0Hz), 6.37(1H,s), 7.20(1H,t,J=8.0Hz), 7.33(2H,d,J=8.4Hz), 7.47(1H,d,
J=8.0Hz), 7.49(1H,s), 7.81(2H,d,J=8.4Hz), 8.54(1H,d,J=7.0Hz), 9.93(1H,s), 10.41(1H,s).
IR(KBr) ν : 3330, 3200, 2920, 1660, 1630, 1610, 1595, 1555, 1540, 1500, 1435, 1380, 1350, 1285, 1255, 1210,
1180, 1160, 1090, 1070, 770, 720, 660 cm⁻¹.

(13) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol-5-yl)-L-glutamine

⁵ $^1\text{H-NMR}(\text{DMSO-d}_6)$ δ : 1.95-2.50(2H,m), 2.60(2H,m), 2.96(4H,m), 4.43(1H,m), 5.88(2H,brs), 6.43(1H,s), 6.52(2H,s), 7.32(2H,d,J=8.4Hz), 7.79(2H,d,J=8.4Hz), 8.54(1H,d,J=8.0Hz), 10.56(1H,s), 11.88(1H,brs).
IR(KBr) ν : 3380, 3270, 3200, 2910, 1680, 1630, 1605, 1540, 1490, 1450, 1380, 1330, 1240, 1155, 1040 cm⁻¹.

Example 10

Production of N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(γ)-hemiphthaloyl-L-¹⁰ 2,4-diaminobutyric acid

In substantially the same manner as in Example 6, 4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid (566 mg) and methyl N(γ)-phthaloyl-L-2,4-diaminobutyrate hydrochloride (625 mg) were subjected to condensation with diethyl cyanophosphate in the presence of triethylamine to afford methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]¹⁵ pyrimidin-5-yl)ethyl]benzoyl]-N(γ)-phthaoyl-L-2,4-diaminobutyrate.

$^1\text{H-NMR}$ (DMSO-d₆) δ : 2.00-2.35(2H,m), 2.97(4H,m), 3.61(3H,s), 4.44(1H,m), 5.57(2H,brs), 6.20(2H,brs), 6.41(1H,s), 7.32(2H,d,J=8.2Hz), 7.75(2H,d,J=8.2Hz), 7.83(4H,s), 8.74(1H,d,J=7.6Hz), 10.49(1H,brs).
²⁰ IR(KBr) ν : 3370, 3200, 1950, 1770, 1735, 1710, 1660, 1610, 1575, 1545, 1500, 1430, 1400, 1200, 1185, 720 cm⁻¹.

The whole amount of the above-mentioned ester was subjected to hydrolysis with sodium hydroxide, in substantially the same manner as in Example 8, to obtain the subject compound (850 mg; yield 82%).
²⁵ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.75-2.20(2H,m), 2.96(4H,brs), 3.32(2H,m), 4.51(1H,m), 5.77(2H,brs), 6.41(3H,brs), 7.32(2H,d,J=8.0Hz), 7.35-7.55(3H,m), 7.70-7.85(3H,m), 8.31(1H,m), 8.53(1H,d,J=7.4Hz), 10.59(1H,brs).

Example 11

Production of N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3,4-methylenedioxybenzoyl)-L-ornithine³⁰

To a DMF solution of 4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoic acid (1.52 g) and methyl ester of N(δ)-t-butyloxycarbonyl-L-ornithine (1.3 g) was added diethyl cyanophosphate (1.4 g). The mixture was stirred for one hour at room temperature in the presence of triethylamine (3.0 g). The reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography on silica gel (carrier:30 g; chloroform:³⁵ ethanol containing 1% ammonium = 20:1 - 15:1) to afford methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(δ)-(t-butyloxycarbonyl)-L-ornithinate (2.30 g; yield 85%).
 $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.37(9H,s), 1.40-1.60(2H,m), 1.70-1.85(2H,m), 2.90-3.15(6H,m), 3.64(3H,s), 4.40(1H,m), 6.61(1H,s), 6.81(1H,t,J=7.0Hz), 6.97(2H,brs), 7.33(2H,d,J=8.2Hz), 7.63(2H,brs), 7.80(2H,d,J=8.2Hz), 8.63(1H,d,J=7.4Hz), 11.35(1H,brs).

⁴⁰ To a dichloromethane (1 ml) solution of the above-mentioned methyl ornithinate (200 mg) was added dropwise, under ice-cooling, trifluoroacetic acid (1 ml), and the mixture was stirred for 20 minutes at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was dissolved in DMF. To the solution were added 3,4-methylenedioxybenzoic acid (68 mg) and ethyl cyanophosphate (150 mg). The mixture was stirred for 10 minutes, to which was added dropwise, under ice-cooling, triethylamine (500 mg), followed by stirring for further⁴⁵ two hours at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography on silica gel (eluent; chloroform : 1% ammonia ethanol = 15:1) to afford methyl N(δ)-(3,4-methylenedioxybenzoyl)-L-ornithinate. The whole amount of this product was dissolved in methanol (6 ml), to which was added, under ice-cooling, an aqueous solution of sodium hydroxide (1 ml), and the mixture was stirred for 5 hours at room temperature. The reaction mixture was concentrated under reduced pressure. The concentrate was⁵⁰ dissolved in water, whose pH was adjusted to 4 with dilute hydrochloric acid. Resulting precipitates were collected by filtration, washed with water and dried under reduced pressure to afford the subject compound (108 mg; yield 51%).

$^1\text{H-NMR}$ (DMSO-d₆) δ : 1.45-1.95(4H,m), 2.96(4H,brs), 3.25(2H,m), 4.39(1H,m), 5.83(2H,brs), 6.09(2H,s), 6.43(1H,s), 6.47(2H,brs), 6.97(1H,d,J=8.4Hz), 7.33(2H,d,J=8.0Hz), 7.38(1H,s), 7.43(1H,d,J=8.4Hz), 7.81(2H,d,J=8.0Hz), 8.33(1H,brt,J=5.2Hz), 8.53(1H,d,J=7.6Hz), 10.63(1H,brs).
⁵⁵ IR(KBr) ν : 3340, 3200, 2930, 1640, 1540, 1500, 1485, 1440, 1400, 1360, 1300, 1260, 1040 cm⁻¹.

Example 12

In substantially the same manner as in Example 11, methyl N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(t-butyloxycarbonyl)-L-ornithinate (1 mmol.) was converted into amino group with trifluoroacetic acid, which was subjected to condensation with diethyl cyanophosphate in the presence of carboxylic acid (1,1 mmol.) and triethylamine, followed by alkali hydrolysis to afford the following compounds:

(1) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxy-2-naphthoyl)-L-ornithine.

¹⁰ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.60-2.05(4H,m), 2.96(4H,brs), 3.35(2H,m), 4.43(1H,m), 5.77(2H,brs), 6.42(3H,brs), 7.32(2H,d,J=8.0Hz), 7.60-7.70(2H,m), 7.83(2H,d,J=8.0Hz), 7.97(1H,s), 7.95-8.15(2H,m), 8.36(1H,s), 8.40-8.60(2H,m), 10.62(1H,brs).

IR(KBr) ν : 3350, 3220, 2930, 1705, 1650, 1540, 1500, 1460, 1380, 1300 cm⁻¹.

(2) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d] pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(2-hydroxybenzoyl)-L-ornithine

¹⁵ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.50-1.95(4H,m), 2.96(4H,brs), 3.33(2H,m), 4.41(1H,m), 5.73(2H,brs), 6.37(3H,brs), 6.41(1H,s), 6.80-6.95(2H,m), 7.32(2H,d,J=8.0Hz), 7.39(1H,m), 7.80(2H,d,J=8.0Hz), 7.84(1H,m), 8.53(1H,d, J=7.8Hz), 8.84(1H,m), 10.57(1H,brs).

IR(KBr) ν : 3340, 3200, 2930, 1640, 1595, 1540, 1490, 1450, 1390, 1300, 1250, 755 cm⁻¹.

(3) N(α)-[4-[3-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)propyl]benzoyl]-N(δ)-(o-pyrrolidinocarbonylbenzoyl)-L-ornithine

²⁵ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.50-2.00(8H,m), 2.97(4H,m), 3.09(2H,t,J=6.4Hz), 3.22(2H,m), 3.38(2H,m), 4.39(1H, m), 5.63(2H,brs), 6.28(2H,brs), 6.40(1H,s), 7.32(2H,d,J=8.2Hz), 7.25-7.65(4H,m), 7.82(2H,d,J=8.2Hz), 8.36 (1H,t,J=5.0Hz), 8.51(1H,d,J=7.8Hz), 10.52(1H,brs).

IR(KBr) ν : 3330, 1610, 1570, 1540, 1490, 1450, 1430cm⁻¹

(4) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(4-carboxybenzoyl)-L-ornithine

³⁰ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.60-2.00(4H,m), 2.96(4H,brs), 3.30(2H,m), 4.41(1H,m), 5.45(2H,brs), 6.09(2H,brs), 6.37(1H,s), 7.33(2H,d,J=8.2Hz), 7.80(2H,d,J=8.2Hz), 7.92(2H,d,J=8.6Hz), 8.00(2H,d,J=8.6Hz), 8.51(1H,d, J=8.0Hz), 8.66(1H,t,J=5.8Hz), 10.41(1H,brs).

IR(KBr) ν : 3330, 3200, 2930, 1640, 1570, 1540, 1500, 1455, 1385, 1290, 1190, 730cm⁻¹.

(5) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3(E)-carboxyl-2-propenoyl)-L-ornithine

³⁵ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.40-1.90(4H,m), 2.96(4H,brs), 3.16(2H,m), 4.32(1H,m), 5.48(2H,brs), 6.12(2H,brs), 6.37(1H,s), 6.51(1H,d,J=15.4Hz), 6.83(1H,d,J=15.4Hz), 7.32(2H,d,J=8.0Hz), 7.78(2H,d,J=8.0Hz), 8.38(1H, d,J=7.4Hz), 8.47(1H,m), 10.42(1H,brs).

IR(KBr) ν : 3325, 3200, 2925, 1645, 1620, 1565, 1540, 1500, 1460, 1390, 1330, 1190, 1090, 975cm⁻¹.

(6) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxylpropionyl)-L-ornithine

⁴⁰ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.40-1.90(4H,m), 2.20-2.50(4H,m), 2.96(4H,brs), 3.05(2H,m), 4.34(1H,m), 5.58(2H, brs), 6.22(2H,brs), 6.39(1H,s), 7.33(2H,d,J=8.2Hz), 7.80(2H,d,J=8.2Hz), 7.86(1H,t,J=7.6Hz), 8.49(1H,d, J=7.4Hz), 10.48(1H,brs).

IR(KBr) ν : 3330, 3200, 2930, 1640, 1545, 1500, 1455, 1400cm⁻¹

(7) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3,4,5-trimethoxybenzoyl)-L-ornithine

⁵⁵ $^1\text{H-NMR}$ (DMSO-d₆) δ : 1.50-2.00(4H,m), 2.95(4H,brs), 3.29(2H,m), 3.69(3H,s), 3.81(6H,s), 4.38(1H,m), 5.45 (2H,brs), 6.08(2H,brs), 6.36(1H,s), 7.17(2H,s), 7.32(2H,d,J=8.2Hz), 7.80(2H,d,J=8.2Hz), 8.40-8.55(2H,m), 10.40(1H,brs).

IR(KBr) ν : 3340, 3200, 2940, 1640, 1590, 1540, 1460, 1410, 1335, 1235, 1185, 1125, 1000, 760cm⁻¹.

(8) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(4-acetamidobenzoyl)-L-ornithine

⁵ ¹H-NMR(DMSO-d₆) δ : 1.45-1.95(4H,m), 2.06(3H,s), 2.96(4H,brs), 3.27(2H,m), 4.39(1H,m), 5.83(2H,brs), 6.43(1H,s), 6.50(2H,brs), 7.33(2H,d,J=8.0Hz), 7.63(2H,d,J=8.4Hz), 7.79(2H,d,J=8.4Hz), 7.81(2H,d,J=8.0Hz), 8.36(1H,m), 8.53(1H,d,J=7.8Hz), 10.16(1H,s), 10.65(1H,brs).

IR(KBr) ν : 3320, 3200, 2930, 1640, 1530, 1500, 1460, 1400, 1370, 1315, 1260, 1180cm⁻¹.

¹⁰ (9) N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(2,6-dimethylbenzoyl)-L-ornithine

¹H-NMR(DMSO-d₆) δ : 1.50-2.00(4H,m), 2.19(6H,s), 2.96(4H,brs), 4.38(1H,m), 5.45(2H,brs), 6.07(2H,brs), 6.36(1H,s), 7.01(2H,d,J=7.8Hz), 7.16(1H,dd,J=8.7,6.4Hz), 7.33(2H,d,J=8.0Hz), 7.79(2H,d,J=8.0Hz), 8.29(1H,t,J=5.0Hz), 8.51(1H,d,J=7.7Hz), 10.40(1H,brs).

IR(KBr) ν : 3330, 3200, 2925, 1640, 1600, 1560, 1540, 1500, 1460, 1400, 1300, 770cm⁻¹.

Example 13

Each of carboxylic acids obtained in Examples 9(1), 9(2), 5(1), 10 and 12(1), respectively, was dissolved in an aqueous solution of sodium hydroxide having the equivalent mole to the carboxylic acid. And the solution was lyophilized to obtain the following sodium salt.

(1) Sodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-borophenyl-L-glutamate

²⁵ ¹H-NMR(DMSO-d₆) δ : 1.85-2.20(2H,m), 2.34(2H,t,J=8.0Hz), 2.95(4H,m), 4.08(1H,m), 5.35(2H,s), 5.95(2H,s), 6.37(1H,s), 7.20(1H,t,J=7.8Hz), 7.32(2H,d,J=8.2Hz), 7.40(1H,d,J=7.8Hz), 7.65-7.80(4H,m), 7.86(1H,d,J=6.2Hz), 10.31(1H,brs), 10.35(1H,brs).

IR(KBr) ν : 3400, 1650, 1610, 1580, 1540, 1490, 1430, 1410, 1340cm⁻¹.

(2) Disodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamate

¹H-NMR(DMSO-d₆) δ : 1.90-2.10(2H,m), 2.32(2H,t,J=7.4Hz), 2.94(4H,m), 4.01(1H,m), 5.34(2H,s), 5.95(2H,s), 6.36(1H,s), 7.13(1H,t,J=7.9Hz), 7.32(2H,d,J=8.2Hz), 7.50(1H,d,J=7.8Hz), 7.65(1H,d,J=7.8Hz), 7.69(2H,d,J=8.2Hz), 7.85(1H,d,J=6.0Hz), 7.91(1H,t,J=1.2Hz), 10.34(1H,s), 10.37(1H,s).

IR(KBr) ν : 3370, 1650, 1610, 1570, 1560, 1545, 1530, 1490, 1430, 1385, 770cm⁻¹.

(3) Disodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithinate

⁴⁰ ¹H-NMR(DMSO-d₆) δ : 1.40-1.60(2H,m), 1.70-2.00(2H,m), 2.94(4H,m), 3.20(2H,m), 4.11(1H,m), 5.36(2H,s), 5.96(2H,s), 6.37(1H,s), 7.20-7.50(5H,m), 7.64(1H,dd,J=7.8,1.8Hz), 7.76(2H,d,J=8.0Hz), 7.96(1H,d,J=6.6Hz), 10.10(1H,brs), 10.37(1H,s).

IR(KBr) ν : 3380, 1610, 1580, 1490, 1430, 1390, 1310, 1190, 1090cm⁻¹.

(4) Disodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(γ)-hemiphthaloyl-L-2,4-diaminobutyrate

⁵⁰ ¹H-NMR(DMSO-d₆) δ : 1.70-2.10(2H,m), 2.95(4H,m), 3.17(2H,m), 4.03(1H,m), 5.34(2H,s), 5.94(2H,s), 6.36(1H,s), 7.15-7.45(5H,m), 7.63(1H,dd,J=7.6,1.4Hz), 7.72(2H,d,J=8.2Hz), 7.88(1H,d,J=6.6Hz), 10.25(1H,brs), 10.34(1H,brs).

IR(KBr) ν : 3390, 1610, 1585, 1550, 1530, 1490, 1430, 1395, 1310cm⁻¹.

(5) Disodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxyl-2-naphthoyl)-L-ornithinate

⁵⁵ ¹H-NMR(DMSO-d₆) δ : 1.40-1.60(2H,m), 1.70-2.10(2H,m), 2.92(4H,m), 3.20(2H,m), 4.15(1H,m), 5.34(2H,s), 5.93(2H,s), 6.36(1H,s), 7.30(2H,d,J=8.0Hz), 7.45-7.55(2H,m), 7.75(2H,d,J=8.0Hz), 7.85-8.00(3H,m), 7.97(1H,s), 8.25(1H,s), 10.35(1H,brs).

IR(KBr) v: 3400, 1685, 1610, 1580, 1550, 1490, 1460, 1435, 1400, 1350, 1325, 1300, 1205, 1180, 1130cm⁻¹

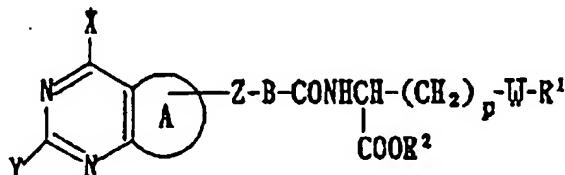
The compounds of this invention have highly specific toxicities to various tumor cells (especially to cells of human lung cancer) and show excellent therapeutic effects on methotrexate-resistant tumor cells as well.

5

Claims

1. A compound of the formula,

10



15

wherein the ring A stands for an optionally hydrogenated 5-membered cyclic group consisting of carbon atoms or carbon atoms and one hetero atom selected from nitrogen, oxygen and sulfur, which group being unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₃₋₈ cycloalkyl group, halogen, a C₁₋₄ alkanoyl group, a benzoyl group (unsubstituted or substituted with 1 to 3 substituents selected from halogen and C₁₋₄ alkoxy), a cyano group, a carboxyl group, a carbamoyl group, a nitro group, a hydroxyl group, a hydroxy-C₁₋₄ alkyl group, a C₁₋₄ alkoxy-C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, a mercapto group, a C₁₋₄ alkylthio group, an amino group (unsubstituted or substituted with one or two C₁₋₄ alkyl groups) and a C₁₋₄ alkanoyl amino group, wherein when the 5-membered cyclic group is an N-substituted pyrrole or N-substituted pyrrolidine, the N-substituted pyrrole and N-substituted pyrrolidine are a pyrrole and pyrrolidine substituted at the nitrogen atom with a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl, a C₃₋₆ cycloalkyl group, a C₁₋₄ alkanoyl group, a benzoyl group (unsubstituted or substituted with 1 to 3 substituents selected from halogen and C₁₋₄ alkoxy) a hydroxy-C₁₋₄ alkyl group, a C₁₋₄ alkoxy-C₁₋₄ alkyl group, a phenyl group (unsubstituted or substituted with 1 to 3 substituents selected from halogen and C₁₋₄ alkoxy) or a benzyl group (unsubstituted or substituted with 1 to 3 substituents selected from halogen, C₁₋₄ alkoxy and phenyl); B stands for a divalent 5 or 6 membered homocyclic group or a heterocyclic group containing one to three hetero atoms selected from nitrogen, oxygen and sulfur, having bonding hands at positions which are not adjacent to each other in the ring, which homocyclic group and heterocyclic group being unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₃₋₈ cycloalkyl group, halogen, a hydroxyl group, a C₁₋₄ alkoxy group, a di-C₁₋₄ alkylamino group, a halogeno-C₁₋₄ alkyl group, oxo, a C₁₋₄ acyl group and a C₁₋₄ alkoxy-C₁₋₄ alkyl group;

X stands for an amino group, a hydroxyl group or a mercapto group;

40

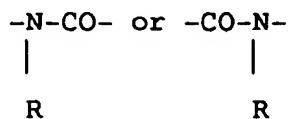
Y stands for

- (1) a hydrogen atom,
- (2) a halogen atom,
- (3) a cyano group,
- (4) a carboxyl group,
- (5) a carbamoyl group,
- (6) an amino group,
- (7) a nitro group,
- (8) a hydroxyl group,
- (9) a mercapto group,
- (10) a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₃₋₈ cycloalkyl group, a C₁₋₄ alkoxy group, a C₁₋₄ alkylthio group, a C₁₋₄ alkylcarbonylamino group or a C₁₋₄ alkyl-carbonyloxy group,
- (11) a C₆₋₁₀ aryl group, a C₆₋₁₀ aryloxy group, a C₆₋₁₀ arylthio group, a C₆₋₁₀ arylcarbonylamino group or a C₆₋₁₀ arylcarbonyloxy group,
- (12) a heterocyclic group, a heterocyclic-oxy group, a heterocyclic-thio group, a heterocyclic-carbonylamino group or a heterocyclic-carbonyloxy group wherein the heterocyclic group or moiety is a 5- or 6- membered heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur,
- (13) an amino group substituted with one or two substituents selected from the group consisting of a C₁₋₄ alkyl

group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₆₋₁₀ aryl group and a 5- or 6-membered heterocyclic group containing 1 to 4 hetero atoms selected from nitrogen, oxygen and sulfur, or
 (14) a group mentioned in the above (10) to (12), which is substituted with one or two substituents selected from the group consisting of a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₃₋₈ cycloalkyl group, halogen, a hydroxyl group, oxo, a C₁₋₄ alkoxy group, a di-C₁₋₄ alkylamino group, a halogeno-C₁₋₄ alkyl group, a C₁₋₄ acyl group, a hydroxy-C₁₋₄ alkyl group, and a C₁₋₄ alkoxy-C₁₋₄ alkyl group;

Z stands for divalent aliphatic group having five or less atoms constituting the straight-chain being a straight-chain aliphatic group selected from C₁₋₅ alkylene, C₂₋₅ alkenylene and C₂₋₅ alkynylene, or a group of the formula: -Z¹-Z²-Z³- wherein Z¹ and Z³ independently stand for a bond, a C₁₋₄ alkylene group, C₂₋₄ alkenylene or C₂₋₄ alkynylene, and Z² stands for -O-, a group of the formula: -S(O)_n- wherein n' denotes an integer of 0 to 2, or a group of the formula: -NR⁴- wherein R⁴ stands for (1) a hydrogen atom, (2) a C₁₋₄ alkoxy-carbonyl group or (3) a C₁₋₄ alkyl group, C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group or a C₃₋₈ cycloalkyl group, wherein the groups represented by Z¹, Z³, (3) in the definition of R⁴, and the straight-chain aliphatic groups are unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, a C₂₋₄ alkynyl group, a C₃₋₈ cycloalkyl group, halogen, a hydroxyl group, oxo, a C₁₋₄ alkoxy group, a di-C₁₋₄ alkylamino group, a halogeno-C₁₋₄ alkyl group, a C₁₋₄ acyl group, a hydroxy-C₁₋₄ alkyl group and a C₁₋₄ alkoxy-C₁₋₄ alkyl group;
 W stands for a group represented by

20

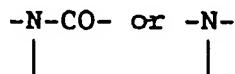


25

wherein R stands for

(1) hydrogen,
 (2) a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group or a C₃₋₄ cycloalkyl group which groups being unsubstituted or substituted by one to three substituents selected from the group consisting of C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, halogen, hydroxy, oxo, C₁₋₄ alkoxy, di-C₁₋₄ alkyl amino, halogeno-C₁₋₄ alkyl, C₁₋₄ acyl, hydroxy-C₁₋₄ alkyl and C₁₋₄ alkoxy-C₁₋₄ alkyl, or
 (3) with R¹, taken together with adjacent

35



40

forms a 3- to 13- membered heterocyclic ring being composed of carbon atoms and one to four hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur which ring being unsubstituted or substituted by one or two substituents selected from the group consisting of C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, halogen, hydroxy, oxo, C₁₋₄ alkoxy, di-C₁₋₄ alkyl amino, halogeno-C₁₋₄ alkyl, C₁₋₄ acyl, hydroxy-C₁₋₄ alkyl and C₁₋₄ alkoxy-C₁₋₄ alkyl; R¹ stands for (1) a C₁₋₄ alkyl, C₂₋₄ alkenyl or C₃₋₄ cycloalkyl, (2) a 5- or 6- membered cyclic hydrocarbon group or 5- or 6- membered heterocyclic group containing one to four hetero atoms selected from nitrogen, oxygen and sulfur, or their condensed cyclic groups being unsubstituted or substituted by one or two substituents selected from the group consisting of C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₆ cycloalkyl, C₅₋₆ cycloalkenyl, C₇₋₈ aralkyl, phenyl, a 5- or 6- membered heterocyclic ring, C₁₋₄ alkoxy, phenoxy, C₁₋₄ alkanoyl, benzoyl, a C₁₋₄ alkanoyloxy, benzoyloxy, carboxyl, C₁₋₄ alkoxy-carbonyl, C₁₋₄ alkoxy carbonyl-C₁₋₄ alkyl, carboxyl-C₁₋₄ alkyl, carbamoyl, N-C₁₋₄ alkyl carbamoyl, 1-aziridinylcarbonyl, 1-azetidinylcarbonyl, 1-pyrrolidinylcarbonyl, 1-piperidinylcarbonyl, N-methylpiperazinylcarbonyl, morpholinocarbonyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N,N-dipropylcarbamoyl and N,N-dibutylcarbamoyl, halogen, mono, di- or tri- halogeno-C₁₋₄ alkyl, oxo, an amidino group, an imino group, an amino group, mono-C₁₋₄ alkylamino, di-C₁₋₄ alkylamino, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, pyrrolyl, imidazolyl, imidazolidinyl, piperidino, morpholino, dihydropyridyl, pyridyl, N-methylpiperazinyl, N-ethylpiperazinyl, C₁₋₄ alkanoylamido, benzamido group, carbamoylamino group, N-C₁₋₄ alkyl carbamoylamino, 1-aziridinylcarbonylamino, 1-azetidinylcarbonylamino, 1-pyrrolidinylcarbonylamino, 1-piperidinylcarbonylamino, N-methyl-

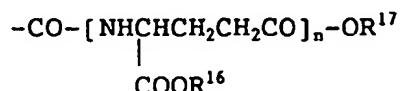
5 piperazinylcarbonylamino, morpholinocarbonylamino, N,N-dimethylcarbamoylamino, N,N-diethylcarbamoylamino, N,N-dipropylcarbamoylamino, N,N-dibutylcarbamoylamino, C₁₋₃ alkylene dioxy, -B(OH)₂, hydroxyl, epoxy (-O-), nitro, cyano, mercapto, sulfo, sulfino, phosphono, dihydroxyboryl, sulfamoyl, C₁₋₄ alkyl sulfamoyl, 1-pyrrolidinylsulfonyl, 1-piperidinylsulfonyl, N-methyl-1-piperazinylsulfonyl and morpholinosulfonyl, di-C₁₋₄ alkyl sulfamoyl, C₁₋₄ alkylthio, phenylthio, C₁₋₄ alkyl sulfinyl, phenylsulfinyl, C₁₋₄ alkyl sulfonyl and phenylsulfonyl, wherein the 5-, or 6-membered heterocyclic ring is unsubstituted or substituted by one or two substituents selected from the group consisting of a C₁₋₄ alkyl group, a C₁₋₄ alkoxy group, halogen, a hydroxyl group, a carboxyl group, a sulfo group, a phosphono group, an amidino group, an amino group, a methylamino group, an ethylamino group, a dimethylamino group, a diethylamino group, a morpholino group, a piperidyl group, a N-methylpiperazinyl group, a pyridyl group, a trimethylammonium group, a triethylammonium group, a pyridinium group, a tetrazolyl group and a carboxymethyl group;

COOR² stands for a carboxyl group or a

- 15 (1) C₁₋₅ alkyl,
(2) benzyl (unsubstituted or substituted by one to three substituents selected from the group consisting of nitro or C₁₋₄ alkoxy group), or
(3) phenyl (unsubstituted or substituted by one to three substituents selected from the group consisting of nitro and C₁₋₄ alkoxy)

20 ester thereof; and
p denotes an integer of 1 to 4;
provided that when -W-R¹ denotes a moiety represented by the formula:

25

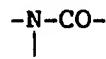


30

(wherein COOR¹⁶ and COOR¹⁷ are, independently, a carboxyl group or an ester thereof as defined for R² and n denotes an integer of 1 to 5), p denotes 1, 3 or 4, or its salt.

- 35 2. A compound as claimed in claim 1, wherein the ring A stands for a cyclopentadiene, cyclopentene, furan, dihydrofuran, thiophene, dihydrothiophene, thiophen-1-oxide, dihydrothiophen-1-oxide, thiophen-1,1-dioxide, dihydrothiophen-1,1-dioxide, pyrrole, pyrroline, N-substituted pyrrole or N-substituted pyrroline being unsubstituted or substituted with 1 or 2 substituents as defined for A in claim 1.
- 40 3. A compound as claimed in claim 1, wherein the ring A stands for a pyrrole, furan or thiophene being unsubstituted or substituted at carbon atom thereof with 1 or 2 substituents as defined for A in claim 1.
4. A compound as claimed in claim 1, wherein the ring A stands for a pyrrole, furan or thiophene.
- 45 5. A compound as claimed in claim 1, wherein B stands for a group selected from cyclopentylene, cyclohexylene, 1,3- or 3,5-cyclopentadien-1,3-ylene, cyclopenten-(1,3-, 1,4- or 3,5-)ylene, cyclopentan-1,3-ylene, phenyl-(1,3- or 1,4-)ylene, cyclohexan-(1,3- or 1,4-)ylene, cyclohexen-(1,3-, 1,4-, 1,5-, 3,5- or 3,6-)ylene, 1,3-cyclohexadien-(1,3-, 1,4-, 1,5-, 2,4- 2,5- or 2,6-)ylene, 1,4-cyclohexadien-(1,3-, 1,4-, or 1,5-)ylene, 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, thiophen-(2,4-, 2,5- or 3,4-)ylene, furan-(2,4-, 2,5- or 3,4-)ylene, pyrrol-(1,3-, 2,4-, 2,5- or 3,4-)ylene, thiazol-(2,4- or 2,5-)ylene, imidazol-(1,4-, 2,4- or 2,5-)ylene, thiadiazol-2,5-ylene, pyridin-(2,4-, 2,5-, 2,6- or 3,5-)ylene, pyran-(2,4-, 2,5-, 2,6-, 3,5-, 3,6-, or 4,6-)ylene, pyrazin-(2,5- or 2,6-)ylene, pyrimidin-(2,4- or 2,5-)ylene, pyridazin-3,5-ylene or a partially or completely reduced derivative thereof, which groups being unsubstituted or substituted with 1 or 2 substituents as defined for B in claim 1.
- 55 6. A compound as claimed in claim 1, wherein B stands for a phenyl-1,4-ylene, thiophen-2,5-ylene thiazol-2,5-ylene or pyridin-2,5-ylene which may be substituted with 1 or 2 substituents as defined for B in claim 1.
7. A compound as claimed in claim 1, wherein B stands for a phenyl-1,4-ylene.

8. A compound as claimed in claim 1, wherein X stands for an amino group or hydroxy group.
9. A compound as claimed in claim 1, wherein X stands for an amino group.
- 5 10. A compound as claimed in claim 1, wherein the 5- or 6-membered heterocyclic group in the definition of Y is pyrrolyl, imidazolyl, pyrazolyl, thieryl, furyl, thiazolyl, thiadiazolyl, oxazolyl, oxadiazolyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl, dioxolanyl, piperidino, morpholino, N-methylpiperazinyl, N-ethylpiperazinyl or dioxanyl.
- 10 11. A compound as claimed in claim 1, wherein Y stands for hydrogen, a C₁₋₄ alkyl group, an amino group or a hydroxyl group.
12. A compound as claimed in claim 1, wherein Y stands for an amino group.
13. A compound as claimed in claim 1, wherein Z stands for a C₁₋₅ alkylene group.
- 15 14. A compound as claimed in claim 1, wherein Z stands for ethylene.
- 15 15. A compound as claimed in claim 1, wherein Z stands for trimethylene.
- 20 16. A compound as claimed in claim 17, wherein Z is -NR⁴-.
17. A compound as claimed in claim 1, wherein Z stands for a group of the formula: -Z'-NR⁴-, wherein R⁴ stands for hydrogen atom, or a C₁₋₄ alkyl group (unsubstituted or substituted by a C₁₋₄ alkoxy-carbonyl group, a formyl group or a C₁₋₄ alkoxy-carbonyl group).
- 25 18. A compound as claimed in claim 1, wherein Z stands for a group of the formula: -(CH₂)₂-NH-, -(CH₂)₂-N(CH₃)- or -(CH₂)-N(Boc)-.
- 30 19. A compound as claimed in claim 1, wherein the 3- to 13-membered ring in the definition of W is selected from pyrrolyl, imidazolyl, pyrazolyl, piperidino, morpholino, dihydropyridyl, tetrahydropyridyl, N-methyl piperazinyl, N-ethyl piperazinyl, azacycloheptyl, azacyclooctyl, isoindolyl, indolyl, 2-pyrrolidinon-1-yl, 2-piperazinon-1-yl, hexahydro-2-azepinon-1-yl, octahydro-2-azocinon-1-yl, 2-oxoindolin-1-yl, 1-oxoisooindolin-2-yl, 2-oxo-1,2,3,4-tetrahydroquinolin-1-yl, 1-oxo-1,2,3,4-tetrahydroisoquinolin-2-yl, 1-oxo-5H-benzo-1,2,3,4-tetrahydro-2-azepin-2-yl, 1-oxabenzo-1,2,3,4,5,6-hexahydro-2-azocin-2-yl, 2-oxo-5H-benzo-1,2,3,4-tetrahydro-1-azepin-1-yl, 2-oxobenzo-1,2,3,4,5,6-hexahydro-1-azocin-1-yl, succinimide, glutarimide, 1,4-butanedicarboximide, 1,5-pentanedicarboximide, 1,2-cyclohexanedicarboximide, phthalimide and partially or completely reduced derivatives thereof, which rings being monocyclic or cyclized with benzene, naphthalene, thiophene, furan, pyrrol, imidazole, pyrazole, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, furazane, pyran, pyridine, pyrazine, pyrimidine, pyridazine or their partially reduced or completely reduced compounds, dioxolan, dioxane, piperidine, morpholine, N-methylpiperazine or N-ethylpiperazine.
- 35 20. A compound as claimed in claim 1, wherein W stands for the group -NHCO-.
21. A compound as claimed in claim 1, wherein W stands for the group -CONH-.
- 40 45 22. A compound as claimed in claim 19, wherein the ring which formed by R with R¹, taken together with adjacent



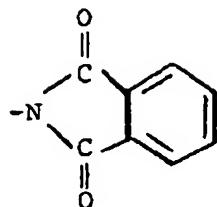
50

or

55

-N-

stands for a group:

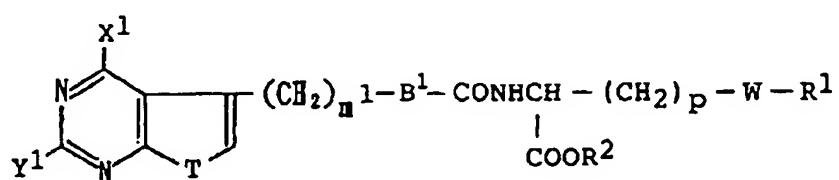


being unsubstituted or substituted by one to three substituents selected from the group consisting of a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₃₋₈ cycloalkyl, halogen, hydroxy, oxo, C₁₋₄ alkoxy, di-C₁₋₄ alkyl amino, halogeno-C₁₋₄ alkyl, C₁₋₄ acyl, hydroxy-C₁₋₄ alkyl and C₁₋₄ alkoxy-C₁₋₄ alkyl.

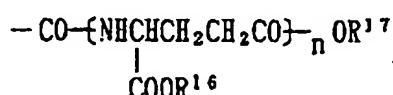
- 15 23. A compound as claimed in claim 1, wherein the 5- or 6-membered cyclic hydrocarbon group in the definition of R¹ stands for cyclopentadienyl, cyclopentenyl, cyclopentyl, cyclohexyl, cyclohexenyl, cyclohexanediyl, phenyl and partially or completely reduced derivatives thereof.
- 20 24. A compound as claimed in claim 1, wherein the 5- or 6-membered heterocyclic group in the definition of R¹ stands for thieryl, furyl, pyrrolyl, thiazoyl, imidazoyl, thiadiazoyl, tetrazoyl, pyridyl, pyranyl, pyrazinyl, pyrimidinyl, pyridazinyl and partially or completely reduced derivatives thereof.
- 25 25. A compound as claimed in claim 1, wherein the condensed cyclic group in the definition of R¹ stands for a naphthyl, indenyl, benzothiazoyl, benzooxazoyl, quinolyl, isoquinolyl, quinazoyl and partially or completely reduced derivatives thereof.
- 30 26. A compound as claimed in claim 1, wherein R¹ stands for a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, phenyl, cyclohexyl, naphthyl, thieryl, cyclopentyl or tetrazoyl being unsubstituted or substituted by one or two substituents as defined for R¹ in claim 1.
- 35 27. A compound as claimed in claim 1, wherein R¹ stands for a C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, phenyl, naphthyl or tetrazoyl being unsubstituted or substituted by substituents selected from the group consisting of hydroxy, carboxyl, -B(OH)₂, tetrazoyl, methylenedioxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy-carbonyl, carboxyl-C₁₋₄ alkyl, C₁₋₄ alkoxy-carbonyl-C₁₋₄ alkyl, C₁₋₄ alkanoylamide and 1-pyrrolidinylcarbonyl.
- 40 28. A compound as claimed in claim 1, wherein R¹ stands for C₁₋₄ alkyl, C₂₋₄ alkenyl or C₂₋₄ alkynyl, being unsubstituted or substituted by substituents selected from the group consisting of carboxyl and C₁₋₄ alkoxy-carbonyl.
- 45 29. A compound as claimed in claim 1, wherein R¹ stands for phenyl, naphthyl or tetrazoyl being unsubstituted or substituted by substituents selected from the group consisting of hydroxy, carboxyl, -B(OH)₂, tetrazoyl, methylenedioxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkoxy-carbonyl, carboxyl-C₁₋₄ alkyl, C₁₋₄ alkoxy-carbonyl-C₁₋₄ alkyl, C₁₋₄ alkanoylamide and 1-pyrrolidinylcarbonyl.
30. A compound as claimed in claim 1, wherein R² stands for
- (1) a C₁₋₅ alkyl group, or
 - (2) a benzyl group.
- 50 31. A compound as claimed in claim 1, wherein COOR² stands for COOH or COOCH₃.
32. A compound as claimed in claim 1, wherein p denotes an integer of 2 to 4.
33. A compound as claimed in claim 1, wherein p denotes 2 or 3.
- 55 34. A compound as claimed in claim 1, wherein X stands for an amino group, and Y stands for an amino group.
35. compound as claimed in claim 1, wherein X stands for an amino group, Y stands for an amino group and ring A

stands for a pyrrole.

36. A compound as claimed in claim 1, wherein X stands for an amino group, Y stands for an amino group, ring A stands for a pyrrole and B stands for a phenyl-1,4-ylene.
 37. A compound as claimed in claim 1, wherein R¹ stands for an optionally substituted cyclic group when p denotes 2 and W stands for the group -CO-NH-.
 38. A compound represented by the formula:

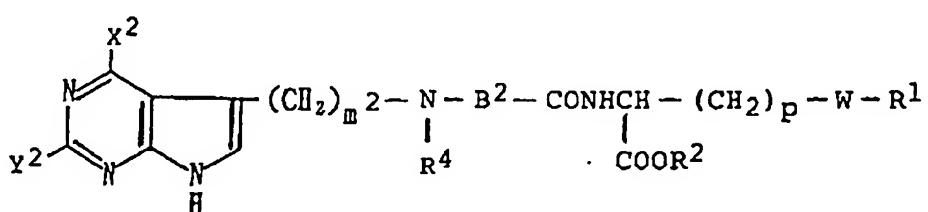


wherein T stands for a nitrogen, oxygen or sulfur atom; B¹ is as B defined in claim 1; X¹ stands for an amino group, a hydroxyl group or a mercapto group; Y¹ is as Y defined in claim 1; W, R¹ and COOR² are as defined in claim 1; m¹ denotes an integer of 1 to 5; and p denotes an integer of 1 to 4, provided that when -W-R¹ denotes a moiety represented by the formula or its salt:

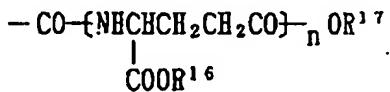


(wherein COOR¹⁶ and COOR¹⁷ are as defined in claim 1 and n denotes an integer of 1 to 5), p denotes 1, 3 or 4,

39. A compound represented by the formula:

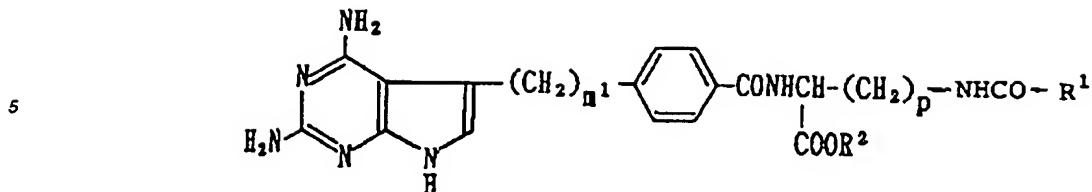


wherein B² is as B defined in claim 1; X² stands for an amino group, a hydroxyl group or a mercapto group; Y² is as Y defined in claim 1; R¹, R⁴, W and COOR² are as defined in claim 1; m² denotes an integer of 1 to 4; and p denotes an integer of 1 to 4, provided that when -W-R¹ denotes a moiety represented by the formula or its salt:



(wherein COOR¹⁶ and COOR¹⁷ are as defined in claim 1 and n denotes an integer of 1 to 5), p denotes 1, 3 or 4.

- 55 40. A compound as claimed in claim 1, which is a compound of the formula:



10 wherein m¹ denotes an integer of 1 to 5; the other symbols are as defined in claim 1, or its salt.

41. A compound as claimed in claim 40, wherein R¹ stands for a phenyl group being unsubstituted or substituted as defined in claim 1.

15 42. A compound as claimed in claim 40, wherein R¹ stands for a phenyl group being unsubstituted or substituted by a carboxyl-C₁₋₄ alkyl group.

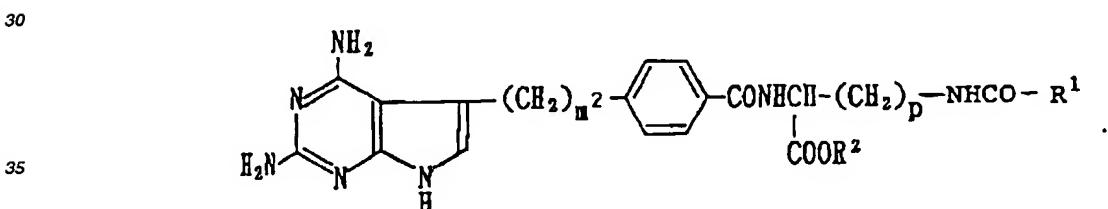
43. A compound as claimed in claim 40, wherein R¹ stands for a naphthyl group being unsubstituted or substituted as defined in claim 1.

20 44. A compound as claimed in claim 40, wherein R¹ stands for a naphthyl group being unsubstituted or substituted by a carboxyl-C₁₋₄ alkyl group.

45. A compound as claimed in claim 40, wherein COOR² stands for a carboxyl group or a C₁₋₄ alkyl ester thereof.

25 46. A compound as claimed in claim 40, wherein p denotes an integer of 2 to 4.

47. A compound as claimed in claim 1, which is a compound of the formula:



35 wherein m² denotes an integer of 1 to 5; the other symbols are as defined in claim 1, or its salt.

40 48. A compound as claimed in claim 47, wherein R¹ stands for a phenyl group being unsubstituted or substituted as defined in claim 1.

49. A compound as claimed in claim 47, wherein R¹ stands for a phenyl group being unsubstituted or substituted by a carboxyl-C₁₋₄ alkyl group.

50 50. A compound as claimed in claim 47, wherein R¹ stands for a naphthyl group being unsubstituted or substituted as defined in claim 1.

51. A compound as claimed in claim 47, wherein R¹ stands for a naphthyl group being unsubstituted or substituted by a carboxyl-C₁₋₄ alkyl group.

52. A compound as claimed in claim 47, wherein COOR² stands for a carboxyl group or a C₁₋₄ alkyl ester thereof.

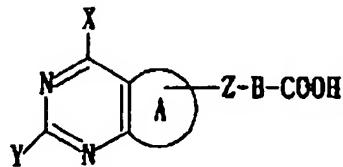
55 53. A compound as claimed in claim 47, wherein R¹ stands for a tetrazolyl group being unsubstituted or substituted as defined in claim 1.

54. A compound as claimed in claim 47, wherein p denotes an integer of 1 to 4.

55. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine or its salt.
56. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamine or its salt.
57. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxy-2-naphthoyl)-L-ornithine or its salt.
58. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol-5-yl)-L-glutamine or its salt.
59. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithine.
60. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamine.
61. Disodium N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamate.
62. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxy-2-naphthoyl)-L-ornithine.
63. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol-5-yl)-L-glutamine.
64. A method of producing a compound claimed in claim 1, which is characterized by allowing a compound represented by the formula:

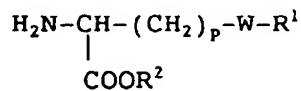
25

30



wherein A, B, X, Y and Z are as defined in claim 1, or, its salt reactive derivative at its carboxyl group to react with a compound represented by the formula:

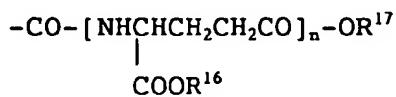
35



40

wherein W, R¹ and COOR² are as defined in claim 1; and p denotes an integer of 1 to 4, provided that when -W-R¹ denotes a moiety represented by the formula:

45



50

(wherein COOR¹⁶ and COOR¹⁷ are as defined in claim 1 and n denotes an integer of 1 to 5), p denotes 1, 3 or 4, or its salt.

55

65. An anti-tumor composition which comprises a compound or its salt as claimed in claim 1.
66. An anti-tumor composition which comprises an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier or carriers.
67. An agent for inhibiting cell-proliferation which comprises an effective amount of a compound as claimed in claim

1 or a pharmaceutically acceptable salt thereof.

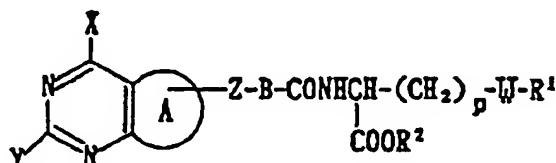
68. An agent for inhibiting human lung cancer cell-proliferation which comprises an effective amount of a compound as claimed in claim 1 or a pharmaceutically acceptable salt thereof.

5

69. Use of a compound as claimed in claim 1 or its pharmaceutically acceptable salt as a component in the preparation of antitumor agent.

10 Patentansprüche

1. Verbindung der Formel



worin der Ring A für eine gegebenenfalls hydrierte, 5-gliedrige, cyclische Gruppe steht, die aus Kohlenstoffatomen oder Kohlenstoffatomen und einem aus Stickstoff, Sauerstoff und Schwefel ausgewählten Heteroatom besteht, wobei die Gruppe unsubstituiert oder mit 1 oder 2 Substituenten substituiert ist, die aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₃₋₈-Cycloalkylgruppe, Halogen, einer C₁₋₄-Alkanoylgruppe, einer Benzoylgruppe (unsubstituiert oder mit 1 bis 3 Substituenten substituiert, die aus Halogen und C₁₋₄-Alkoxy ausgewählt sind), einer Cyanogruppe, einer Carboxylgruppe, einer Carbamoylgruppe, einer Nitrogruppe, einer Hydroxylgruppe, einer Hydroxy-C₁₋₄-alkylgruppe, einer C₁₋₄-Alkoxy-C₁₋₄-alkylgruppe, einer C₁₋₄-Alkoxygruppe, einer Mercaptogruppe, einer C₁₋₄-Alkylthiogruppe, einer Aminogruppe (unsubstituiert oder mit einer oder zwei C₁₋₄-Alkylgruppen substituiert) und einer C₁₋₄-Alkanoylaminogruppe besteht, wobei, wenn die 5-gliedrige cyclische Gruppe ein N-substituiertes Pyrrol oder N-substituiertes Pyrrolin ist, das N-substituierte Pyrrol und N-substituierte N-Pyrrolin ein Pyrrol und Pyrrolin sind, die am Stickstoffatom mit einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₃₋₈-Cycloalkylgruppe, einer C₁₋₄-Alkanoylgruppe, einer Benzoylgruppe (unsubstituiert oder mit 1 bis 3 Substituenten substituiert, die aus Halogen und C₁₋₄-Alkoxy ausgewählt sind), einer Hydroxylgruppe, einer C₁₋₄-Alkoxy-C₁₋₄-alkylgruppe, einer Phenylgruppe (unsubstituiert oder mit 1 bis 3 Substituenten substituiert, die aus Halogen und C₁₋₄-Alkoxy ausgewählt sind), oder einer Benzylgruppe (unsubstituiert oder mit 1 bis 3 Substituenten substituiert, die aus Halogen, C₁₋₄-Alkoxy und Phenyl ausgewählt sind) substituiert sind; B für eine zweiwertige, 5- oder 6-gliedrige homocyclische Gruppe oder eine heterocyclische Gruppe steht, die ein bis drei aus Stickstoff, Sauerstoff und Schwefel ausgewählte Heteroatome enthält und zwei freie Bindungen in Stellungen besitzt, die einander im Ring nicht benachbart sind, wobei die homocyclische Gruppe und heterocyclische Gruppe unsubstituiert oder mit 1 oder 2 Substituenten substituiert ist, die aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₃₋₈-Cycloalkylgruppe, Halogen, einer Hydroxylgruppe, einer C₁₋₄-Alkoxygruppe, einer Di-C₁₋₄-alkylaminogruppe, einer Halogen-C₁₋₄-alkylgruppe, Oxo, einer C₁₋₄-Acylgruppe und einer C₁₋₄-Alkoxy-C₁₋₄-alkylgruppe besteht;

X für eine Aminogruppe, eine Hydroxylgruppe oder eine Mercaptogruppe steht;

Y für

- 50 (1) ein Wasserstoffatom,
 (2) ein Halogenatom,
 (3) eine Cyanogruppe,
 (4) eine Carboxylgruppe,
 (5) eine Carbamoylgruppe,
 (6) eine Aminogruppe,
 (7) eine Nitrogruppe,
 (8) eine Hydroxylgruppe,
 (9) eine Mercaptogruppe,
 (10) eine C₁₋₄-Alkylgruppe, eine C₂₋₄-Alkenylgruppe, eine C₂₋₄-Alkinylgruppe, eine C₃₋₈-Cycloalkylgruppe, ei-

ne C₁₋₄-Alkoxygruppe, eine C₁₋₄-Alkylthiogruppe, eine C₁₋₄-Alkylcarbonylaminogruppe oder eine C₁₋₄-Alkylcarbonyloxygruppe,

(11) eine C₆₋₁₀-Arylgruppe, eine C₆₋₁₀-Aryloxygruppe, eine C₆₋₁₀-Arylthiogruppe, eine C₆₋₁₀-Arylcarbonylaminogruppe oder eine C₆₋₁₀-Arylcarbonyloxygruppe,

5 (12) eine heterocyclische Gruppe, eine Heterocyclooxygruppe, eine Heterocyclothiogruppe, eine Heterocyclocarbonylaminogruppe oder eine Heterocyclocarbonyloxygruppe, wobei die heterocyclische Gruppe-oder Struktureinheit eine 5- oder 6-gliedrige heterocyclische Gruppe ist, die 1 bis 4 Heteroatome enthält, welche aus Stickstoff, Sauerstoff und Schwefel ausgewählt sind,

10 (13) eine Aminogruppe, die mit einem oder zwei Substituenten substituiert ist, welche aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₆₋₁₀-Arylgruppe und einer 5- oder 6-gliedrigen heterocyclischen Gruppe besteht, welche 1 bis 4 Heteroatome ent-hält, die aus Stickstoff, Sauerstoff und Schwefel ausgewählt sind, oder

15 (14) eine vorstehend in (10) bis (12) angeführte Gruppe steht, die mit einem oder zwei Substituenten substi-tuiert ist, welche aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₃₋₈-Cycloalkylgruppe, Halogen, einer Hydroxylgruppe, Oxo, einer C₁₋₄-Alkoxygruppe, einer Di-C₁₋₄-alkylaminogruppe, einer Halogen-C₁₋₄-alkylgruppe, einer C₁₋₄-Acylgruppe, einer Hy-droxy-C₁₋₄-alkylgruppe und einer C₁₋₄-Alkoxy-C₁₋₄-alkylgruppe besteht;

20 Z für eine zweiwertige aliphatische Gruppe mit fünf oder weniger Atomen steht, welche die gerade Kette darstellen, die eine geradkettige aliphatische Gruppe, welche aus C₁₋₅-Alkylen, C₂₋₅-Alkenylen und C₂₋₅-Alkinylen ausgewählt ist, oder eine Gruppe der Formel -Z¹-Z²-Z³- ist, worin Z¹ und Z³ unabhängig für eine Bindung, eine C₁₋₄-Alkenylen-gruppe, C₂₋₄-Alkenylen oder C₂₋₄-Alkinylen stehen und Z² für -O-, eine Gruppe der Formel -S(O)_n-, worin n' eine 25 ganze Zahl 0 bis 2 bezeichnet, oder eine Gruppe der Formel -NR⁴- steht, worin R⁴ für (1) ein Wasserstoffatom, (2) eine C₁₋₄-Alkoxy carbonylgruppe oder (3) eine C₁₋₄-Alkylgruppe, C₂₋₄-Alkenylgruppe, eine C₂₋₄-Alkinylgruppe oder eine C₃₋₈-Cycloalkylgruppe steht, wobei die durch Z¹, Z³, (3) dargestellten Gruppen bei der Definition von R⁴ und die geradkettigen aliphatischen Gruppen unsubstituiert oder mit 1 oder 2 Substituenten substituiert sind, die aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₂₋₄-Alkenylgruppe, einer C₂₋₄-Alkinylgruppe, einer C₃₋₈-Cycloalkylgruppe, Halogen, einer Hydroxylgruppe, Oxo, einer C₁₋₄-Alkoxygruppe, einer Di-C₁₋₄-alkylaminogruppe, einer Halogen-C₁₋₄-alkylgruppe, einer C₁₋₄-Acylgruppe, einer Hydroxy-C₁₋₄-alkylgruppe und einer C₁₋₄-Alkoxy-C₁₋₄-alkylgruppe besteht;

30 W für eine durch

-N-CO- oder -CO-N-



35 dargestellte Gruppe steht,
40 worin R für

(1) Wasserstoff,

(2) eine C₁₋₄-Alkylgruppe, eine C₂₋₄-Alkenylgruppe oder eine C₃₋₈-Cycloalkylgruppe steht, wobei die Gruppen unsubstituiert oder durch einen bis drei Substituenten substituiert sind, die aus der Gruppe ausgewählt sind, welche aus C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, C₃₋₈-Cycloalkyl, Halogen, Hydroxy, Oxo, C₁₋₄-Alkoxy, Di-C₁₋₄-alkylamino, Halogen-C₁₋₄-alkyl, C₁₋₄-Acyl, Hydroxy-C₁₋₄-alkyl und C₁₋₄-Alkoxy-C₁₋₄-alkyl besteht, oder (3) mit R¹ zusammengenommen mit benachbartem

50 -N-CO- oder -N-



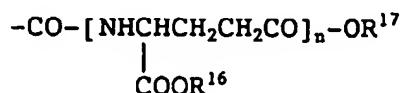
55 einen 3- bis 13-gliedrigen heterocyclischen Ring bildet, der sich aus Kohlenstoffatomen und einem bis vier Heteroatomen zusammensetzt, welche aus der Gruppe ausgewählt sind, die aus Stickstoff, Sauerstoff und Schwefel besteht, wobei der Ring unsubstituiert oder durch einen oder zwei Substituenten substituiert ist, welche aus der Gruppe ausgewählt sind, die aus C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, C₃₋₈-Cycloalkyl, Ha-logen, Hydroxy, Oxo, C₁₋₄-ASoxy, Di-C₁₋₄-alkylamino, Halogen-C₁₋₄-alkyl, C₁₋₄-Acyl, Hydroxy-C₁₋₄-alkyl und C₁₋₄-Alkoxy-C₁₋₄-alkyl besteht; R¹ für (1) eine C₁₋₄-Alkyl-, C₂₋₄-Alkenyl- oder C₃₋₈-Cycloalkyl-, (2) eine 5- oder

6-gliedrige cyclische Kohlenwasserstoffgruppe oder 5- oder 6-gliedrige heterocyclische Gruppe, die ein bis vier aus Stickstoff, Sauerstoff und Schwefel ausgewählte Heteroatome enthält, oder ihre kondensierten cyclischen Gruppen, die unsubstituiert oder durch einen oder zwei Substituenten substituiert sind, die aus der Gruppe ausgewählt sind, die aus C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, C₃₋₆-Cycloalkyl, C₅₋₆-Cycloalkenyl, C₇₋₈-Aralkyl, Phenyl, einem 5- oder 6-gliedrigen heterocyclischen Ring, C₁₋₄-Alkoxy, Phenoxy, C₁₋₄-Alkanoyl, Benzoyl, C₁₋₄-Alkanoyloxy, Benzoyloxy, Carboxyl, C₁₋₄-Alkoxy carbonyl, C₁₋₄-Alkoxy carbonyl-C₁₋₄-alkyl, Carboxy-C₁₋₄-alkyl, Carbamoyl, N-C₁₋₄-Alkyl carbamoyl, 1-Aziridinyl carbonyl, 1-Azetidinyl carbonyl, 1-Pyrrolidinyl carbonyl, 1-Piperidinyl carbonyl, N-Methylpiperazinyl carbonyl, Morpholinocarbonyl, N,N-Dimethylcarbamoyl, N,N-Diethylcarbamoyl, N,N-Dipropylcarbamoyl und N,N-Dibutylcarbamoyl, Halogen, Mono-, Di- oder Trihalogen-C₁₋₄-alkyl, Oxo, einer Amidinogruppe, einer Iminogruppe, einer Aminogruppe, Mono-C₁₋₄-alkylamino, Di-C₁₋₄-alkylamino, Aziridinyl, Azetidinyl, Pyrrolidinyl, Pyrrolinyl, Pyrazolyl, Imidazolidinyl, Piperidino, Morpholino, Dihydroxyridyl, Pyridyl, N-Methylpiperazinyl, N-Ethylpiperazinyl, C₁₋₄-Alkanoylamido, Benzimidogruppe, Carbamoylaminogruppe, N-C₁₋₄-Alkyl carbamoylamino, 1-Aziridinyl carbonylamino, 1-Azetidinyl carbonylamino, 1-Pyrrolidinyl carbonylamino, 1-Piperidinyl carbonylamino, N-Methylpiperazinyl carbonylamino, Morpholinocarbonylamino, N,N-Dimethylcarbamoylamino, N,N-Diethylcarbamoylamino, N,N-Dipropylcarbamoylamino, N,N-Dibutylcarbamoylamino, C₁₋₃-Alkylendioxy, -B(OH)₂, Hydroxyl, Epoxy (-O-), Nitro, Cyano, Mercapto, Sulfo, Sulfino, Phosphono, Dihydroxyboryl, Sulfamoyl, C₁₋₄-Alkylsulfamoyl, 1-Pyrrolidinylsulfonyl, 1-Piperidinylsulfonyl, N-Methyl-1-piperazinylsulfonyl und Morpholinosulfonyl, Di-C₁₋₄-alkylthio, Phenylthio, C₁₋₄-Alkylsulfinyl, Phenylsulfinyl, C₁₋₄-Alkylsulfonyl und Phenylsulfonyl besteht, wobei der 5- oder 6-gliedrige heterocyclische Ring unsubstituiert oder durch einen oder zwei Substituenten substituiert ist, welche aus der Gruppe ausgewählt sind, die aus einer C₁₋₄-Alkylgruppe, einer C₁₋₄-Alkoxygruppe, Halogen, einer Hydroxylgruppe, einer Carboxylgruppe, einer Sulfogruppe, einer Phosphonogruppe, einer Amidinogruppe, einer Aminogruppe, einer Methylaminogruppe, einer Ethylaminogruppe, einer Dimethylaminogruppe, einer Diethylaminogruppe, einer Morpholinogruppe, einer Piperidylgruppe, einer N-Methylpiperazylgruppe, einer Pyridylgruppe, einer Trimethylammoniumgruppe, einer Triethylammoniumgruppe, einer Pyridiniumgruppe, einer Tetrazolylgruppe und einer Carboxymethylgruppe besteht;

COOR² für eine Carboxylgruppe oder deren

- (1) C₁₋₅-Alkyl,
- (2) Benzyl- (unsubstituiert oder durch einen bis drei Substituenten substituiert, welche aus der Gruppe ausgewählt sind, die aus Nitro oder einer C₁₋₄-Alkoxygruppe besteht) oder
- (3) Phenylester (unsubstituiert oder durch einen bis drei Substituenten substituiert, welche aus der Gruppe ausgewählt sind, die aus Nitro und C₁₋₄-Alkoxy besteht) steht, und

p eine ganze Zahl 1 bis 4 bezeichnet,
vorausgesetzt, daß wenn -W-R¹ eine durch die Formel



dargestellte Struktureinheit bedeutet (worin COOR¹⁶ und COOR¹⁷ unabhängig eine Carboxylgruppe oder ein wie für R² definierter Ester derselben sind und n eine ganze Zahl 1 bis 5 bezeichnet), p 1, 3 oder 4 bezeichnet, oder ihr Salz.

2. Verbindung wie in Anspruch 1 beansprucht, wobei der Ring A für ein Cyclopentadien, Cyclopenten, Furan, Dihydrofuran, Thiophen, Dihydrothiophen, Thiophen-1-oxid, Dihydrothiophen-1-oxid, Thiophen-1,1-dioxid, Dihydrothiophen-1,1-dioxid, Pyrrol, Pyrrolin, N-substituiertes Pyrrol oder N-substituiertes Pyrrolin steht, die unsubstituiert oder mit 1 oder 2 für A in Anspruch 1 definierten Substituenten substituiert sind.
3. Verbindung wie in Anspruch 1 beansprucht, wobei der Ring A für ein Pyrrol, Furan oder Thiophen steht, die unsubstituiert oder an einem Kohlenstoffatom derselben mit 1 oder 2 für A in Anspruch 1 definierten Substituenten substituiert sind.
4. Verbindung wie in Anspruch 1 beansprucht, wobei der Ring A für ein Pyrrol, Furan oder Thiophen steht.

5. Verbindung wie in Anspruch 1 beansprucht, wobei B für eine Gruppe steht, die aus Cyclopentylen, Cyclohexylen, 1,3- oder 3,5-Cyclopentadien-1,3-ylen, Cyclopenten-(1,3-, 1,4- oder 3,5-)ylen, Cyclopantan-1,3-ylen, Phenyl-(1,3- oder 1,4-)ylen, Cyclohexan-(1,3- oder 1,4-)ylen, Cyclohexen-(1,3-, 1,4-, 1,5-, 3,5- oder 3,6-)ylen, 1,3-Cyclohexadien-(1,3-, 1,4-, 1,5-, 2,4-, 2,5- oder 2,6-)ylen, 1,4-Cyclohexadien-(1,3-, 1,4- oder 1,5-)ylen, 1,2-Phenylen, 1,3-Phenylen, 1,4-Phenylen, Thiophen-(2,4-, 2,5- oder 3,4-)ylen, Furan-(2,4-, 2,5- oder 3,4-)ylen, Pyrrol-(1,3-, 2,4-, 2,5- oder 3,4-)ylen, Thiazol-(2,4- oder 2,5-)ylen, Imidazol-(1,4-, 2,4- oder 2,5-)ylen, Thiadiazol-2,5-ylen, Pyridin-(2,4-, 2,5-, 2,6- oder 3,5-)ylen, Pyran-(2,4-, 2,5-, 2,6-, 3,5-, 3,6- oder 4,6-)ylen, Pyrazin-(2,5- oder 2,6-)ylen, Pyrimidin-(2,4- oder 2,5-)ylen, Pyridazin-3,5-ylen oder ein teilweise oder vollständig reduziertes Derivat derselben steht, wobei die Gruppen unsubstituiert oder mit 1 oder 2 für B in Anspruch 1 definierten Substituenten substituiert sind.
- 10 6. Verbindung wie in Anspruch 1 beansprucht, wobei B für Phenyl-1,4-ylen, Thiophen-2,5-ylen, Thiazol-2,5-ylen oder Pyridin-2,5-ylen steht, die mit 1 oder 2 für B in Anspruch 1 definierten Substituenten substituiert sein können.
- 15 7. Verbindung wie in Anspruch 1 beansprucht, wobei B für Phenyl-1,4-ylen steht.
8. Verbindung wie in Anspruch 1 beansprucht, wobei X für eine Aminogruppe oder Hydroxygruppe steht.
- 10 9. Verbindung wie in Anspruch 1 beansprucht, wobei X für eine Aminogruppe steht.
- 20 10. Verbindung wie in Anspruch 1 beansprucht, wobei die 5- oder 6-gliedrige heterocyclische Gruppe in der Definition von Y Pyrrolyl, Imidazolyl, Pyrazolyl, Thienyl, Furyl, Thiazolyl, Thiadiazolyl, Oxazolyl, Oxadiazolyl, Pyridyl, Pyranyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl, Dioxolanyl, Piperidino, Morpholino, N-Methylpiperazinyl, N-Ethylpiperazinyl oder Dioxanyl ist.
- 25 11. Verbindung wie in Anspruch 1 beansprucht, wobei Y für Wasserstoff, eine C₁₋₄-Alkylgruppe, eine Aminogruppe oder eine Hydroxylgruppe steht.
12. Verbindung wie in Anspruch 1 beansprucht, wobei Y für eine Aminogruppe steht.
- 30 13. Verbindung wie in Anspruch 1 beansprucht, wobei Z für eine C₁₋₅-Alkylengruppe steht.
14. Verbindung wie in Anspruch 1 beansprucht, wobei Z für Ethylen steht.
- 35 15. Verbindung wie in Anspruch 1 beansprucht, wobei Z für Trimethylen steht.
16. Verbindung wie in Anspruch 17 beansprucht, wobei Z -NR⁴⁻ ist.
- 40 17. Verbindung wie in Anspruch 1 beansprucht, wobei Z für eine Gruppe der Formel -Z¹-NR⁴' steht, worin R⁴ für ein Wasserstoffatom oder eine C₁₋₄-Alkylgruppe (unsubstituiert oder durch eine C₁₋₄-Alkoxy carbonylgruppe, eine Formylgruppe oder eine C₁₋₄-Alkoxy carbonylgruppe substituiert) steht.
18. Verbindung wie in Anspruch 1 beansprucht, wobei Z für eine Gruppe der Formel -(CH₂)₂-NH-, -(CH₂)₂-N(CH₃)- oder -(CH₂)-N(Boc) steht.
- 45 19. Verbindung wie in Anspruch 1 beansprucht, wobei der 3- bis 13-gliedrige Ring in der Definition von W aus Pyrrolyl, Imidazolyl, Pyrazolyl, Piperidino, Morpholino, Dihydropyridyl, Tetrahydropyridyl, N-Methylpiperazinyl, N-Ethylpiperazinyl, Azacycloheptyl, Azacyclooctyl, Isoindolyl, Indolyl, 2-Pyrrolidinon-1-yl, 2-Piperazinon-1-yl, Hexahydro-2-azepinon-1-yl, Octahydro-2-azocinon-1-yl, 2-Oxoindolin-1-yl, 1-Oxoisoindolin-2-yl, 2-Oxo-1,2,3,4-Tetrahydrochinolin-1-yl, 1-Oxo-1,2,3,4-tetrahydroisochinolin-2-yl, 1-Oxo-5H-benzo-1,2,3,4-tetrahydro-2-azepin-2-yl, 1-Oxo-benzo-1,2,3,4,5,6-hexahydro-2-azocin-2-yl, 2-Oxo-5H-benzo-1,2,3,4-tetrahydro-1-azepin-1-yl, 2-Oxobenzo-1,2,3,4,5,6-hexahydro-1-azocin-1-yl, Succinimid, Glutarimid, 1,4-Butandicarboximid, 1,5-Pentandicarboximid, 1,2-Cyclohexanddicarboximid, Phthalimid und teilweise oder vollständig reduzierte Derivate derselben ausgewählt ist, wobei die Ringe monocyclisch oder mit Benzol, Naphthalin, Thiophen, Furan, Pyrrol, Imidazol, Pyrazol, Thiazol, Isothiazol, Thiadiazol, Oxazol, Isoxazol, Oxadiazol, Furazan, Pyran, Pyridin, Pyrazin, Pyrimidin, Pyridazin oder den teilweise reduzierten oder vollständig reduzierten Verbindungen, Dioxolan, Dioxan, Piperidin, Morphin, N-Methylpiperazin oder N-Ethylpiperazin kondensiert sind.
- 55 20. Verbindung wie in Anspruch 1 beansprucht, wobei W für die Gruppe -NHCO- steht.

21. Verbindung wie in Anspruch 1 beansprucht, wobei W für die Gruppe -CONH- steht.
22. Verbindung wie in Anspruch 19 beansprucht, wobei der Ring, der durch R mit R¹ zusammengenommenen mit benachbartem

5

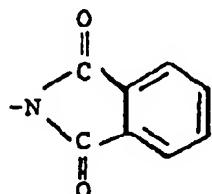
-N-CO- oder -N-

| |

10

gebildet wird, für eine Gruppe

15



20

steht, die unsubstituiert oder durch einen bis drei Substituenten substituiert ist, welche aus der Gruppe ausgewählt sind, die aus C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, C₃₋₈-Cycloalkyl, Halogen, Hydroxy, Oxo, C₁₋₄-Alkoxy, Di-C₁₋₄-alkylamino, Halogen-C₁₋₄-alkyl, C₁₋₄-Acyl, Hydroxy-C₁₋₄-alkyl und C₁₋₄-Alkoxy-C₁₋₄-alkyl besteht.

25

23. Verbindung wie in Anspruch 1 beansprucht, wobei die 5- oder 6-gliedrige cyclische Kohlenwasserstoffgruppe in der Definition von R¹ für Cyclopentadienyl, Cyclopentenyl, Cyclopentyl, Cyclohexyl, Cyclohexenyl, Cyclohexadienyl, Phenyl und teilweise oder vollständig reduzierte Derivate derselben steht.

30

24. Verbindung wie in Anspruch 1 beansprucht, wobei die 5- oder 6-gliedrige heterocyclische Kohlenwasserstoffgruppe in der Definition von R¹ für Thienyl, Furyl, Pyrrolyl, Thiazolyl, Imidazolyl, Thiadiazolyl, Tetrazolyl, Pyridyl, Pyranyl, Pyrazinyl, Pyrimidinyl, Pyridazinyl und teilweise oder vollständig reduzierte Derivate derselben steht.

35

25. Verbindung wie in Anspruch 1 beansprucht, wobei die kondensierte cyclische Gruppe in der Definition von R¹ für Naphthyl, Indenyl, Benzothiazolyl, Benzoxazolyl, Chinolyl, Isochinolyl, Chinazolyl und teilweise oder vollständig reduzierte Derivate derselben steht.

40

26. Verbindung wie in Anspruch 1 beansprucht, wobei R¹ für C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, Phenyl, Cyclohexyl, Naphthyl, Thienyl, Cyclopentyl oder Tetrazolyl steht, die unsubstituiert oder durch einen oder zwei für R¹ in Anspruch 1 definierte Substituenten substituiert sind.

45

27. Verbindung wie in Anspruch 1 beansprucht, wobei R¹ für C₁₋₄-Alkyl, C₂₋₄-Alkenyl, C₂₋₄-Alkinyl, Phenyl, Naphthyl oder Tetrazolyl steht, die unsubstituiert oder durch Substituenten substituiert sind, welche aus der Gruppe ausgewählt sind, die aus Hydroxy, Carboxyl, -B(OH)₂, Tetrazolyl, Methylendioxy, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, C₁₋₄-Alkoxy-carbonyl, Carboxy-C₁₋₄-alkyl, C₁₋₄-Alkoxy carbonyl-C₁₋₄-alkyl, C₁₋₄-Alkanoylamid und 1-Pyrrolidinylcarbonyl besteht.

50

28. Verbindung wie in Anspruch 1 beansprucht, wobei R¹ für C₁₋₄-Alkyl, C₂₋₄-Alkenyl oder C₂₋₄-Alkinyl steht, die unsubstituiert oder durch Substituenten substituiert sind, welche aus der Gruppe ausgewählt sind, die aus Carboxyl und C₁₋₄-Alkoxy carbonyl besteht.

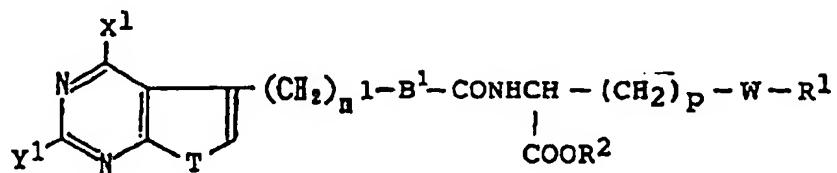
55

29. Verbindung wie in Anspruch 1 beansprucht, wobei R¹ für Phenyl, Naphthyl oder Tetrazolyl steht, die unsubstituiert oder durch Substituenten substituiert sind, welche aus der Gruppe ausgewählt sind, die aus Hydroxy, Carboxyl, -B(OH)₂, Tetrazolyl, Methylendioxy, C₁₋₄-Alkyl, C₁₋₄-Alkoxy, C₁₋₄-Alkoxy carbonyl, Carboxy-C₁₋₄-alkyl, C₁₋₄-Alkoxy carbonyl-C₁₋₄-alkyl, C₁₋₄-Alkanoylamid und 1-Pyrrolidinylcarbonyl besteht.

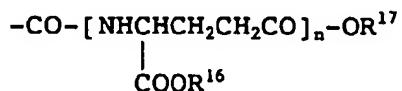
30. Verbindung wie in Anspruch 1 beansprucht, wobei R² für

- (1) eine C₁₋₅-Alkylgruppe oder
 (2) eine Benzylgruppe steht.

31. Verbindung wie in Anspruch 1 beansprucht, wobei COOR² für COOH oder COOCH₃ steht.
 5
 32. Verbindung wie in Anspruch 1 beansprucht, wobei p eine ganze Zahl 2 bis 4 bezeichnet.
 33. Verbindung wie in Anspruch 1 beansprucht, wobei p 2 oder 3 bezeichnet.
 10 34. Verbindung wie in Anspruch 1 beansprucht, wobei X für eine Aminogruppe steht und Y für eine Aminogruppe steht.
 35. Verbindung wie in Anspruch 1 beansprucht, wobei X für eine Aminogruppe steht, Y für eine Aminogruppe steht und Ring A für ein Pyrrol steht.
 15 36. Verbindung wie in Anspruch 1 beansprucht, wobei X für eine Aminogruppe steht, Y für eine Aminogruppe steht, Ring A für ein Pyrrol steht und B für ein Phenyl-1,4-ylen steht.
 20 37. Verbindung wie in Anspruch 1 beansprucht, wobei R¹ für eine gegebenenfalls substituierte cyclische Gruppe steht, wenn p 2 bezeichnet und W für die Gruppe -CO-NH- steht.
 38. Verbindung, die durch die Formel

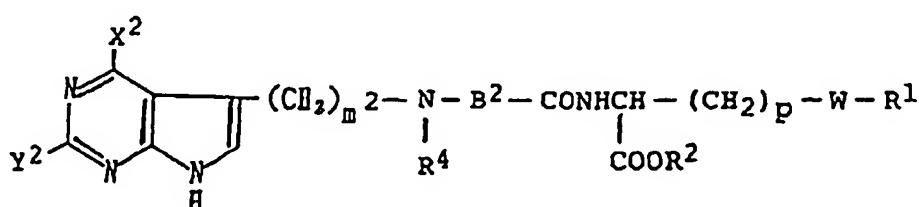


30 dargestellt wird, oder ihr Salz, worin T für ein Stickstoff-, Sauerstoff- oder Schwefelatom steht, B¹ in Anspruch 1 definiertes B ist, X¹ für eine Aminogruppe, eine Hydroxylgruppe oder eine Mercaptogruppe steht, Y¹ in Anspruch 1 definiertes Y ist, W, R¹ und COOR² wie in Anspruch 1 definiert sind, m¹ eine ganze Zahl bis 4 bezeichnet und p eine ganze Zahl 1 bis 4 bezeichnet, vorausgesetzt, daß wenn -W-R¹ eine durch die Formel

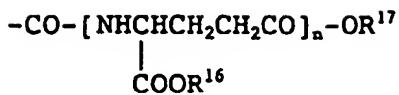


40 dargestellte Struktureinheit bezeichnet (worin COOR¹⁶ und COOR¹⁷ wie in Anspruch 1 definiert sind und n eine ganze Zahl 1 bis 5 bezeichnet), p 1, 3 oder 4 bezeichnet.

- 45 39. Verbindung, die durch die Formel



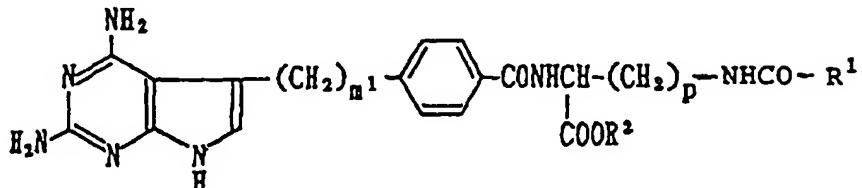
55 dargestellt wird, oder ihr Salz, worin B² in Anspruch 1 definiertes B ist, X² für eine Aminogruppe, eine Hydroxylgruppe oder eine Mercaptogruppe steht, Y² in Anspruch 1 definiertes Y ist, R¹, R⁴, W und COOR² wie in Anspruch 1 definiert sind, m² eine ganze Zahl 1 bis 5 bezeichnet und p eine ganze Zahl 1 bis 4 bezeichnet, vorausgesetzt, daß wenn -W-R¹ eine durch die Formel



5

dargestellte Struktureinheit bezeichnet (worin COOR¹⁶ und COOR¹⁷ wie in Anspruch 1 definiert sind und n eine ganze Zahl 1 bis 5 bezeichnet), p 1, 3 oder 4 bezeichnet.

- 10 40. Verbindung wie in Anspruch 1 beansprucht, die eine Verbindung der Formel



20

ist, worin m¹ eine ganze Zahl 1 bis 5 bezeichnet, die anderen Symbole wie in Anspruch 1 definiert sind, oder ihr Salz.

41. Verbindung wie in Anspruch 40 beansprucht, wobei R¹ für eine Phenylgruppe steht, die unsubstituiert oder wie in Anspruch 1 definiert substituiert ist.

25

42. Verbindung wie in Anspruch 40 beansprucht, wobei R¹ für eine Phenylgruppe steht, die unsubstituiert oder durch eine Carboxy-C₁₋₄-alkylgruppe substituiert ist.

30

43. Verbindung wie in Anspruch 40 beansprucht, wobei R¹ für eine Naphthylgruppe steht, die unsubstituiert oder wie in Anspruch 1 definiert substituiert ist.

35

44. Verbindung wie in Anspruch 40 beansprucht, wobei R¹ für eine Naphthylgruppe steht, die unsubstituiert oder durch eine Carboxy-C₁₋₄-alkylgruppe substituiert ist.

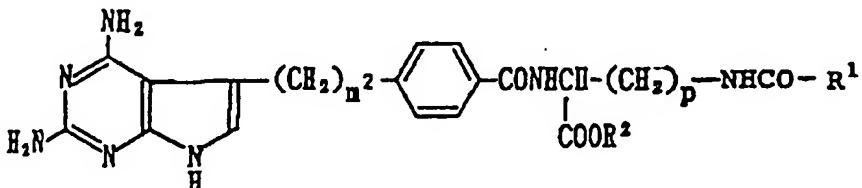
40

45. Verbindung wie in Anspruch 40 beansprucht, wobei COOR² für eine Carboxylgruppe oder einen C₁₋₄-Alkylester derselben steht.

46. Verbindung wie in Anspruch 40 beansprucht, wobei p eine ganze Zahl 2 bis 4 bezeichnet.

40

47. Verbindung wie in Anspruch 1 beansprucht, die eine Verbindung der Formel



50

ist, worin m² eine ganze Zahl 1 bis 5 bezeichnet, die anderen Symbole wie in Anspruch 1 definiert sind, oder ihr Salz.

55

48. Verbindung wie in Anspruch 47 beansprucht, wobei R¹ für eine Phenylgruppe steht, die unsubstituiert oder wie in Anspruch 1 definiert substituiert ist.

55

49. Verbindung wie in Anspruch 47 beansprucht, wobei R¹ für eine Phenylgruppe steht, die unsubstituiert oder durch eine Carboxy-C₁₋₄-alkylgruppe substituiert ist.

50. Verbindung wie in Anspruch 47 beansprucht, wobei R¹ für eine Naphthylgruppe steht, die unsubstituiert oder wie

in Anspruch 1 definiert substituiert ist.

51. Verbindung wie in Anspruch 47 beansprucht, wobei R¹ für eine Naphthylgruppe steht, die unsubstituiert oder durch eine Carboxy-C₁₋₄-alkylgruppe substituiert ist.

5 52. Verbindung wie in Anspruch 47 beansprucht, wobei COOR² für eine Carboxylgruppe oder einen C₁₋₄-Alkylester derselben steht.

10 53. Verbindung wie in Anspruch 47 beansprucht, wobei R¹ für eine Tetrazolylgruppe steht, die unsubstituiert oder wie in Anspruch 1 definiert substituiert ist.

54. Verbindung wie in Anspruch 47 beansprucht, wobei p eine ganze Zahl 1 bis 4 bezeichnet.

15 55. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithin oder sein Salz.

56. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamin oder sein Salz.

20 57. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxy-2-naphthoyl)-L-ornithin oder sein Salz.

58. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol-5-yl)-L-glutamin oder sein Salz.

25 59. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-hemiphthaloyl-L-ornithin.

60. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutamin.

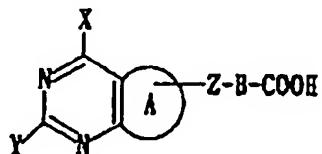
30 61. Dinatrium-N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(3-carboxyphenyl)-L-glutaminat.

62. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N(δ)-(3-carboxy-2-naphthoyl)-L-ornithin.

35 63. N(α)-[4-[2-(2,4-Diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-N-(1H-tetrazol-5-yl)-L-glutamin.

64. Verfahren zum Herstellen einer in Anspruch 1 beanspruchten Verbindung oder ihres Salzes, welches dadurch gekennzeichnet ist, daß man eine durch die Formel

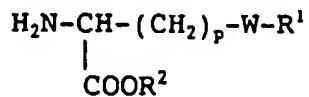
40



45

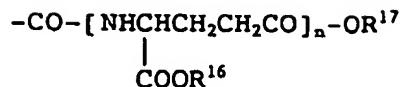
dargestellte Verbindung, worin A, B, X, Y und Z wie in Anspruch 1 definiert sind, oder ihr reaktionsfähiges Salz-derivat an ihrer Carboxylgruppe mit einer durch die Formel

50



55

dargestellten Verbindung reagieren läßt, worin W, R¹ und COOR² wie in Anspruch 1 definiert sind und p eine ganze Zahl 1 bis 4 bezeichnet, vorausgesetzt, daß wenn -W-R¹ eine durch die Formel



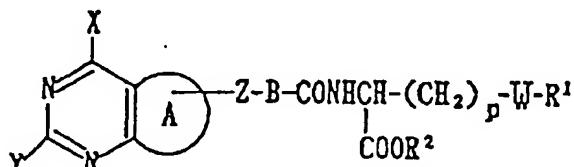
5

dargestellte Struktureinheit bezeichnet (worin COOR^{16} und COOR^{17} wie in Anspruch 1 definiert sind und n eine ganze Zahl 1 bis 5 bezeichnet), p 1, 3 oder 4 bezeichnet.

65. Anti-Tumor-Zusammensetzung, die eine in Anspruch 1 beanspruchte Verbindung oder ihr Salz umfaßt.
- 10 66. Anti-Tumor-Zusammensetzung, die eine wirksame Menge einer in Anspruch 1 beanspruchten Verbindung oder eines pharmazeutisch annehmbaren Salzes derselben zusammen mit einem pharmazeutisch annehmbaren Träger oder Trägern umfaßt.
- 15 67. Mittel zum Hemmen der Zellvermehrung, welches eine wirksame Menge einer in Anspruch 1 beanspruchten Verbindung oder eines pharmazeutisch annehmbaren Salzes derselben umfaßt.
- 20 68. Mittel zum Hemmen der Vermehrung menschlicher Lungenkrebszellen, welches eine wirksame Menge einer in Anspruch 1 beanspruchten Verbindung oder eines pharmazeutisch annehmbaren Salzes derselben umfaßt.
69. Verwendung einer in Anspruch 1 beanspruchten Verbindung oder ihres pharmazeutisch annehmbaren Salzes als Bestandteil bei der Anti-Tumormittelherstellung.

25 **Revendications**

1. Composé de formule



dans laquelle

le cycle A représente un groupe cyclique à 5 chaînons éventuellement hydrogéné constitué d'atomes de carbone ou d'atomes de carbones et d'un hétéroatome choisi parmi les atomes d'azote, d'oxygène et de soufre, lequel groupe est non substitué ou porte 1 ou 2 substituants choisis dans le groupe formé par les résidus alkyle en C_{1-4} , alcényle en C_{2-4} , alcyne en C_{2-4} , cycloalkyle en C_{3-8} , halogéno, alcanoyle en C_{1-4} , benzoyle (non substitué ou portant 1 à 3 substituants choisis parmi un atome d'halogène et les résidus alcoxy en C_{1-4}), cyano, carboxyle, carbamoyle, nitro, hydroxyle, hydroxy(alkyle en C_{1-4}), (alcoxy en C_{1-4})-(alkyle en C_{1-4}), alcoxy en C_{1-4} , mercapto, alkylthio en C_{1-4} , amino (non substitué ou portant 1 ou 2 substituants alkyle en C_{1-4}) et (alcanoyle en C_{1-4})-amino, dans lequel lorsque le groupe cyclique à 5 chaînons est un noyau pyrrole N-substitué ou pyrroline N-substitué, les noyaux pyrrole N-substitué et pyrroline N-substitué sont des noyaux pyrrole et pyrroline portant sur l'atome d'azote un groupe alkyle en C_{1-4} , alcényle en C_{2-4} , alcyne en C_{2-4} , cycloalkyle en C_{3-6} alcanoyle en C_{1-4} , benzoyle (non substitué ou portant de 1 à 3 substituants choisis parmi les atomes d'halogène et les résidus alcoxy en C_{1-4}), hydroxy(alkyle en C_{1-4}), (alcoxy en C_{1-4})-(alkyle en C_{1-4}), phényle (non substitué ou portant de 1 à 3 substituants choisis parmi les atomes d'halogène et les groupes alcoxy en C_{1-4}), ou un groupe benzyle (non substitué ou portant de 1 à 3 substituants choisis parmi les atomes d'halogène, les résidus alcoxy en C_{1-4} et phényle), B représente un groupe homocyclique divalent à 5 ou 6 chaînons ou un groupe hétérocyclique divalent contenant 1 à 3 hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre, avec des bras de liaison en des positions qui ne sont pas adjacentes les unes aux autres sur le cycle, lesquels groupes homocycliques et hétérocycliques sont non substitués ou substitués par 1 ou 2 substituants choisis dans le groupe formé par les résidus alkyle en C_{1-4} , alcényle en C_{2-4} , alcyne en C_{2-4} , cycloalkyle en C_{3-8} , halogéno, hydroxyle, alcoxy en C_{1-4} , di(alkyle en C_{1-4})-amino, halogéno(alkyle en C_{1-4}), oxo, (acyl en C_{1-4}) et (alcoxy en C_{1-4})-(alkyle en C_{1-4}), X représente un groupe amino, un groupe hydroxyle ou un groupe mercapto,

Y représente

- (1) un atome d'hydrogène,
- (2) un atome d'halogène,
- (3) un groupe cyano,
- (4) un groupe carboxyle,
- (5) un groupe carbamoyle,
- (6) un groupe amino,
- (7) un groupe nitro,
- (8) un groupe hydroxyle,
- (9) un groupe mercapto,
- (10) un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, cycloalkyle en C₃₋₈, alcoxy en C₁₋₄, alkylthio en C₁₋₄, (alkyle en C₁₋₄)-carbonylamino ou un groupe (alkyle en C₁₋₄)-carbonyloxy,
- (11) un groupe aryle en C₆₋₁₀, un groupe aryloxy en C₆₋₁₀, un groupe arylthio en C₆₋₁₀, un groupe (aryle en C₆₋₁₀)-carbonylamino ou (aryle en C₆₋₁₀)-carbonyloxy,
- (12) un groupe hétérocyclique, un groupe hétérocyclique-oxy, un groupe hétérocyclique-thio, un groupe hétérocycliquecarbonylamino ou un groupe hétérocyclique-carbonyloxy, où le groupe ou fragment hétérocyclique est un groupe hétérocyclique à 5 ou 6 chaînons contenant de 1 à 4 hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre,
- (13) un groupe amino portant 1 ou 2 substituants choisis dans le groupe formé par les résidus alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, aryle en C₆₋₁₀ et un groupe hétérocyclique à 5 ou 6 chaînons contenant de 1 à 4 hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre,
- (14) un groupe figurant sous (10) à (12) ci-dessus, ce groupe portant 1 ou 2 substituants choisis dans l'ensemble formé par les résidus alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, cycloalkyle en C₃₋₈, halogéno, hydroxyle, oxo, alcoxy en C₁₋₄, di(alkyle en C₁₋₄)-amino, halogénoalkyle en C₁₋₄, acyle en C₁₋₄, hydroxyalkyle en C₁₋₄ et (alcoxy en C₁₋₄)-(alkyle en C₁₋₄).

Z représente un groupe aliphatique divalent comportant 5 ou moins d'atomes de carbone formant la chaîne linéaire qui est un groupe à chaîne linéaire aliphatique choisi parmi les résidus alkylène en C₁₋₅, alcénylène en C₂₋₅ et alcynylène en C₂₋₅, ou un résidu de formule -Z¹-Z²-Z³ où Z¹ et Z³ représentent, indépendamment l'un de l'autre, une liaison directe, un groupe alkylène en C₁₋₄, alcénylène en C₂₋₄ ou alcynylène en C₂₋₄ et Z² représente un groupe -O-, un groupe de formule -S(O)_n- où n' représente un nombre entier compris entre 0 et 2, ou un groupe de formule : -NR⁴- où R⁴ représente (1) un atome d'hydrogène, (2) un groupe (alcoxy en C₁₋₄)-carbonyle ou (3) un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, ou un groupe cycloalkyle en C₃₋₈ où les groupes représenté par Z¹, Z³, (3) dans la définition de R⁴, et les groupes aliphatiques à chaîne linéaire sont non substitués ou portent 1 ou 2 substituants choisis dans l'ensemble formé par un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, cycloalkyle en C₃₋₈ halogéno, hydroxyle, oxo, alcoxy en C₁₋₄, di(alkyle en C₁₋₄)-amino, halogénoalkyle en C₁₋₄, acyle en C₁₋₄, hydroxyalkyle en C₁₋₄ et (alcoxy en C₁₋₄)-(alkyle en C₁₋₄),

W représente un groupe de formule -N(-R)-CO- ou -CO-N(R)- où R représente

- (1) un atome d'halogène,
- (2) un résidu alkyle en C₁₋₄, alcényle en C₂₋₄ ou alcynyle en C₂₋₄, lesquels groupes sont non substitués ou portent de 1 à 3 substituants choisis parmi les résidus alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, cycloalkyle en C₃₋₈ halogéno, hydroxy, oxo, alcoxy en C₁₋₄, di(alkyle en C₁₋₄)-amino, halogénoalkyle en C₁₋₄, acyle en C₁₋₄, hydroxyalkyle en C₁₋₄ et (alcoxy en C₁₋₄)-(alkyle en C₁₋₄), ou
- (3) forme avec R¹, conjointement avec les résidus -N-CO ou -N- adjacents, un hétérocycle comportant de 3 à 13 chaînons constitués d'atomes de carbone et de 1 à 4 hétéroatomes choisis dans l'ensemble formé par les atomes d'azote, d'oxygène et de soufre, lequel cycle est non substitué ou porte 1 ou 2 substituants choisis dans le groupe formé par les résidus alkyle en C₁₋₄, alcényle en C₂₋₄, alcynyle en C₂₋₄, cycloalkyle en C₃₋₈ halogéno, hydroxyle, oxo, alcoxy en C₁₋₄, di(alkyle en C₁₋₄)-amino, halogénoalkyle en C₁₋₄, acyle en C₁₋₄, hydroxyalkyle en C₁₋₄ et (alcoxy en C₁₋₄)-(alkyle en C₁₋₄);

R¹ représente

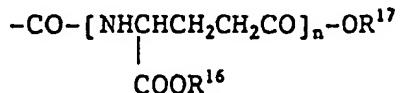
- (1) un groupe alkyle en C₁₋₄, alcényle en C₂₋₄ ou cycloalkyle en C₃₋₄,
- (2) un groupe hydrocarboné cyclique à 5 ou 6 chaînons ou un groupe hétérocyclique à 5 ou 6 chaînons contenant de 1 à 4 hétéroatomes choisis parmi les atomes d'azote, d'oxygène et de soufre, ou les groupes cycliques condensés correspondants non substitués ou substitués par 1 ou 2 substituants choisis dans l'ensemble

formé par les résidus alkyle en C₁₋₄, alcényle en C₂₋₄ alcynyle en C₂₋₄ cycloalkyle en C₃₋₈ cycloalcényle en C₅₋₆, aralkyle en C₇₋₈, phényle, un hétérocycle à 5 ou 6 chaînons, un groupe alcoxy en C₁₋₄, phénoxy, alcanoyle en C₁₋₄, benzoyle, alcanoxyloxy en C₁₋₄, benzoxyloxy, carboxyle, (alcoxy en C₁₋₄)-carbonyle, (alcoxy en C₁₋₄)-carbonyl-(alkyle en C₁₋₄), carboxy(alkyle en C₁₋₄), carbamoyle, N-(alkyle en C₁₋₄)-carbamoyle, 1-aziridinylcarbonyle, 1-azétidinylcarbonyle, 1-pyrrolidinylcarbonyle, 1-pipéridinylcarbonyle, N-méthylpipérazinylcarbonyle, morpholinocarbonyle, N,N-diméthylcarbamoyle, N,N-diéthylcarbamoyle, N,N-dipropylcarbamoyle et N,N-di-butylcarbamoyle, halogéno, mono-, di- ou trihalogéno(alkyle en C₁₋₄), oxo, amidino, imino, amino, mono(alkyle en C₁₋₄)-amino, di(alkyle en C₁₋₄)-amino, aziridinyle, azétidinyle, pyrrolidinyle, pyrrolyne, pyrrolyle, imidazolyle, pyrazolyde, imidazolidinyle, pipéridino, morpholino, dihydropyridyle, pyridyle, N-méthylpipérazinyle, N-éthylpipérazinyle, (alcanoyle en C₁₋₄)-amido, benzamido, carbamoylamino, N-(alkyle en C₁₋₄)-carbamoylamino, 1-aziridinylcarbonylamino, 1-azétidinylcarbonylamino, 1-pyrrolidinylcarbonylamino, 1-pipéridinylcarbonylamino, N-méthylpipérazinylcarbonylamino, morpholinocarbonylamino, N,N-diméthylcarbamoylamino, N,N-diéthylcarbamoylamino, N,N-dipropylcarbamoylamino, N,N-dibutylcarbamoylamino, (alkylène en C₁₋₃)dioxy, -B(OH)₂, hydroxyle, époxy (-O-), nitro, cyano, mercapto, sulfo, sulfino, phosphono, dihydroxyboryle, sulfamoyle, (alkyle en C₁₋₄)sulfamoyle, 1-pyrrolidinylsulfonyle, 1-pipéridinylsulfonyle, N-méthyl-1-pipérazinylsulfonyle et morpholinosulfonyle, di(alkyle en C₁₋₄)-sulfamoyle, (alkyle en C₁₋₄)-thio, phénylthio, (alkyle en C₁₋₄)-sulfynyle, phénylsulfynyle, (alkyle en C₁₋₄)-sulfonyle et phénylsulfonyle, où l'hétérocycle à 5 ou 6 chaînons est non substitué ou porte 1 ou 2 substituants choisis dans l'ensemble formé par un groupe alkyle en C₁₋₄, alcoxy en C₁₋₄, halogéno, hydroxyle, carboxyle, sulfo, phosphono, amidino, amino, méthylamino, éthylamino, diméthylamino, diéthylamino, morpholino, pipéridyle, N-méthylpipérazyle, pyridyle, triméthylammonium, triéthylammonium, pyridinium, tétrazolyde et carboxyméthyle,

COOR² représente un groupe carboxyle ou un ester

- (1) d'alkyle en C₁₋₅,
- (2) de benzyle (non substitué ou portant de 1 à 3 substituants choisis dans le groupe formé par les résidus nitro ou alcoxy en C₁₋₄), ou
- (3) de phényle (non substitué ou portant de 1 à 3 substituants choisis dans le groupe formé par les résidus nitro ou alcoxy en C₁₋₄), de ces composés, et

p représente un nombre entier compris entre 1 et 4,
à condition que p vaille 1, 3 ou 4, lorsque -W-R¹ représente un fragment de formule



dans laquelle COOR¹⁶ et COOR¹⁷ représentent, indépendamment l'un de l'autre, un groupe carboxyle ou l'ester correspondant défini pour R² et n représente un nombre entier compris entre 1 et 5, ou le sel d'un tel composé.

2. Composé conforme à la revendication 1, dans lequel le cycle A représente un groupe cyclopentadiène, cyclopentène, furane, dihydrofurane, thiophène, dihydrothiophène, thiophén-1-oxyde, dihydrothiophén-1-oxyde, thiophén-1,1-dioxyde, dihydrothiophén-1,1-dioxyde, pyrrole, pyrroline, pyrrole ou pyrroline N-substitués, lesquels groupes sont non substitués ou portent de 1 à 2 substituants de ceux définis pour A dans la revendication 1.
3. Composé conforme à la revendication 1, dans lequel le cycle A représente un groupe pyrrole, furane ou thiophène non substitués ou portant sur les atomes de carbone, 1 ou 2 substituants de ceux définis pour A dans la revendication 1.
4. Composé conforme à la revendication 1, dans lequel le cycle A représente un résidu pyrrole, furane ou thiophène.
5. Composé conforme à la revendication 1 dans lequel B représente un groupe choisi parmi les résidus cyclopentylène, cyclohexylène, 1,3- ou 3,5-cyclopentadién-1,3-ylène, cyclopentén-(1,3-, 1,4- ou 3,5)ylène, cyclopentan-1,3-ylène, phényl-(1,3- ou 1,4-)ylène, cyclohexan-(1,3- ou 1,4-)ylène, cyclohexén-(1,3-, 1,4-, 1,5-, 3,5- ou 3,6-)ylène, 1,3-cyclohexadién-(1,3-, 1,4-, 1,5-, 2,4-, 2,5- ou 2,6-)ylène, 1,4-cyclohexadién-(1,3-, 1,4- ou 1,5-)ylène, 1,2-phénylène, 1,3-phénylène, 1,4-phénylène, thiophén-(2,4-, 2,5- ou 3,4-)ylène, furan-(2,4-, 2,5- ou 3,4-)ylène, pyrrol-(1,3-, 2,4-, 2,5- ou 3,4-)ylène, thiazol-(2,4- ou 2,5-)ylène, imidazol-(1,4-, 2,4-, 2,5-, 2,6- ou 3,5-)ylène, pyran-

(2,4-, 2,5-, 2,6-, 3,5-, 3,6-ou 4,6)ylène, pyrazin-(2,5- ou 2,6-)ylène, pyrimidin-(2,4- ou 2,5-)ylène, pyridazin-3,5-ylène ou des dérivés partiellement ou complètement réduits de ces résidus, lesquels résidus peuvent être non substitués ou porter 1 ou 2 substituants de ceux définis pour B dans la revendication 1.

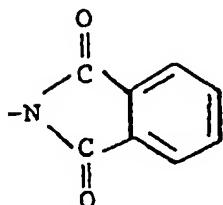
- 5 6. Composé conforme à la revendication 1, dans lequel B représente un groupe phényl-1,4-ylène, thiophén-2,5-ylène, thiazol-2,5-ylène ou pyridin-2,5-ylène éventuellement substitués par 1 ou 2 substituants de ceux définis pour B dans la revendication 1.
- 10 7. Composé conforme à la revendication 1, dans lequel B représente un résidu phényl-1,4-ylène.
- 8. Composé conforme à la revendication 1 dans lequel X représente un groupe amino ou hydroxy.
- 9. Composé conforme à la revendication 1 dans lequel X représente un groupe amino.
- 15 10. Composé conforme à la revendication 1 dans lequel le groupe hétérocyclique à 5 ou 6 chaînons dans la définition de Y est un groupe pyrrolyle, imidazolyle, pyrazolyle, thiényl, furyle, thiazolyle, thiadiazolyle, oxazolyle, oxadiazolyle, pyridyle, pyranyle, pyrazinyle, pyrimidinyle, pyridazinyle, dioxoranyle, pipéridino, morpholino, N-méthylpipérazinyle, N-éthylpipérazinyle ou dioxanyl.
- 20 11. Composé conforme à la revendication 1 dans lequel Y représente un atome d'hydrogène, un groupe alkyle en C₁₋₄, amino ou hydroxyle.
- 12. Composé conforme à la revendication 1 dans lequel Y représente un groupe amine.
- 25 13. Composé conforme à la revendication 1 dans lequel Z représente un groupe alkylène en C₁₋₅.
- 14. Composé conforme à la revendication 1 dans lequel Z représente un résidu éthylène.
- 15. Composé conforme à la revendication 1 dans lequel Z représente un résidu triméthylène.
- 30 16. Composé conforme à la revendication 1 dans lequel Z représente un groupe -NR⁴⁻.
- 17. Composé conforme à la revendication 1 dans lequel Z représente un groupe de formule -Z¹-NR⁴⁻ où R⁴ représente un atome d'hydrogène ou un groupe alkyle en C₁₋₄ (non substitué ou portant un substituant (alcoxy en C₁₋₄)-carbonyle), formyle, ou (alcoxy en C₁₋₄)-carbonyle.
- 35 18. Composé conforme à la revendication 1 dans lequel Z représente un groupe de formule -(CH₂)₂-NH-, -(CH₂)₂N(CH₃)- ou -(CH₂)-N(Boc)-.
- 40 19. Composé conforme à la revendication 1 dans lequel le cycle comportant de 3 à 13 chaînons dans la définition de W est choisi parmi les résidus pyrrolyle, imidazolyle, pyrazolyle, pipéridino, morpholino, dihydropyridyle, tétrahydronpyridyle, N-méthylpipérazinyle, N-éthylpipérazinyle, azacycloheptyle, azacyclooctyle, isoindolyle, indolyle, 2-pyrrolidinon-1-yle, 2-pipérazinon-1-yle, hexahydro-2-azépinon-1-yle, octahydro-2-azocinon-1-yle, 2-oxoindolin-1-yle, 1-oxoisooindolin-2-yle, 2-oxo-1,2,3,4-tétrahydroquinolin-1-yle, 1-oxo-1,2,3,4-tétrahydroisoquinolin-2-yle, 1-oxo-5H-benzo-1,2,3,4-tétrahydro-2-azépin-2-yle, 1-oxobenzo-1,2,3,4,5,6-hexahydro-2-azocin-2-yle, 2-oxo-5H-benzo-1,2,3,4-tétrahydro-1-azépin-1-yle, 2-oxobenzo-1,2,3,4,5,6-hexahydro-1-azocin-1-yle, succinimide, glutarimide, 1,4-butanedicarboximide, 1,5-pentanedicarboximide, 1,2-cyclohexanedicarboximide, phtalimide et des dérivés partiellement ou complètement réduits de ces groupes, lesquels cycles comportant un seul noyau ou étant condensés avec des résidus benzène, naphtalène, thiophène, furane, pyrrole, imidazole, pyrazole, thiazole, isothiazole, thiadiazole, oxazole, isoxazole, oxadiazole, furazane, pyrane, pyridine, pyrazine, pyrimidine, pyridazine, ou leur dérivés partiellement ou complètement réduits, dioxolane, dioxane, pipéridine, morpholine, N-méthylpipérazine ou N-éthylpipérazine.
- 45 20. Composé conforme à la revendication 1 dans lequel W représente le groupe -NHCO-.
- 50 21. Composé conforme à la revendication 1 dans lequel W représente le groupe -CONH-.
- 55 22. Composé conforme à la revendication 19 dans lequel le cycle formé par R et R¹ en conjonction avec le groupe



5

adjacent représente un groupe

10



15

non substitué ou portant de 1 à 3 substituants choisis dans le groupe formé par les résidus alkyle en C₁₋₄, alcényle en C₂₋₄, alcyne en C₂₋₄, cycloalkyle en C₃₋₈ halogéno, hydroxyle, oxo, alcoxy en C₁₋₄, di(alkyle en C₁₋₄)amino, halogénoalkyle en C₁₋₄, acyle en C₁₋₄, hydroxyalkyle en C₁₋₄ et (alcoxy en C₁₋₄)-(alkyle en C₁₋₄).

20

23. Composé conforme à la revendication 1 dans lequel le groupe hydrocarboné cyclique à 5 ou 6 chaînons dans la définition de R¹ est un groupe cyclopentadiényle, cyclopentényle, cyclopentyle, cyclohexyle, cyclohexényle, cyclohexanediényle, phényle et les dérivés partiellement ou complètement réduits de ceux-ci.

25

24. Composé conforme à la revendication 1 dans lequel le groupe hétérocyclique à 5 ou 6 chaînons dans la définition de R¹ est un groupe thiényle, furyle, pyrrolyle, thiazolyle, imidazolyle, thiadiazolyle, tétrazolyle, pyridyle, pyranyle, pyrazinyle, pyrimidinyle, pyridazinyle et les dérivés partiellement ou complètement réduits de ceux-ci.

30

25. Composé conforme à la revendication 1 dans lequel le groupe cyclique condensé dans la définition de R¹ est un groupe naphtyle, indényle, benzothiazolyle, benzoxazolyle, quinolyle, isoquinolyle, quinazolyle et les dérivés partiellement ou complètement réduits de ceux-ci.

35

26. Composé conforme à la revendication 1 dans lequel R¹ représente un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcyne en C₂₋₄, phényle, cyclohexyle, naphtyle, thiényle, cyclopentyle ou tétrazolyle non substitués ou portant un ou deux substituants définis comme pour R¹ dans la revendication 1.

40

27. Composé conforme à la revendication 1 dans lequel R¹ représente un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcyne en C₂₋₄, phényle, naphtyle ou tétrazolyle non substitués ou portant des substituants choisis dans l'ensemble formé par les résidus hydroxy, carboxyle, -B(OH)₂, tétrazolyle, méthylènedioxy, alkyle en C₁₋₄, alcoxy en C₁₋₄, (alcoxy en C₁₋₄)-carbonyle, carboxyl(alkyle en C₁₋₄), (alcoxy en C₁₋₄)-carbonyl-(alkyle en C₁₋₄), (alcanoyle en C₁₋₄)-amide et 1-pyrrolidinylcarbonyle.

45

28. Composé conforme à la revendication 1 dans lequel R¹ représente un groupe alkyle en C₁₋₄, alcényle en C₂₋₄, alcyne en C₂₋₄ non substitués ou portant des substituants choisis dans le groupe formé par les résidus carboxyle et (alcoxy en C₁₋₄)-carbonyle.

50

29. Composé conforme à la revendication 1 dans lequel R¹ représente un résidu phényle, naphtyle ou tétrazolyle non substitués ou portant un substituant choisi dans l'ensemble formé par les résidus hydroxy, carboxyle, -B(OH)₂, tétrazolyle, méthylènedioxy, alkyle en C₁₋₄, alcoxy en C₁₋₄, (alcoxy en C₁₋₄)-carbonyle, carboxyl(alkyle en C₁₋₄), (alcoxy en C₁₋₄)-carbonyl-(alkyle en C₁₋₄), (alcanoyle en C₁₋₄)-amide et 1-pyrrolidinylcarbonyle.

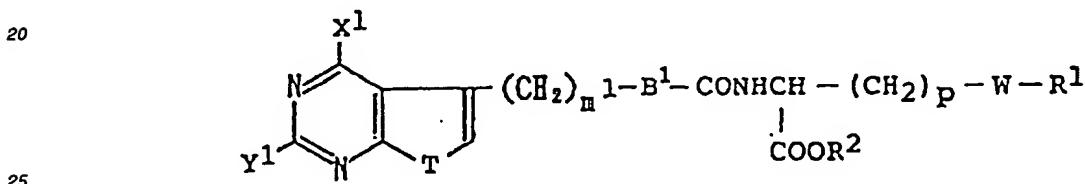
30. Composé conforme à la revendication 1 dans lequel R² représente

55

- (1) un groupe alkyle en C₁₋₅, ou
- (2) un groupe benzyle.

31. Composé conforme à la revendication 1 où COOR² représente un résidu COOH ou COOCH₃.

32. Composé conforme à la revendication 1 dans lequel p représente un nombre entier entre 2 et 4.
33. Composé conforme à la revendication 1 dans lequel p vaut 2 ou 3.
- 5 34. Composé conforme à la revendication 1 dans lequel X représente un groupe amino et Y représente un groupe amino.
- 10 35. Composé conforme à la revendication 1 dans lequel X représente un groupe amino, Y représente un groupe amino et le cycle A représente un noyau pyrrole.
- 15 36. Composé conforme à la revendication 1 dans lequel X représente un groupe amino, Y représente un groupe amino, le cycle A représente un noyau pyrrole et B représente un noyau phényl-1,4-ylène.
37. Composé conforme à la revendication 1 dans lequel R¹ représente un groupe cyclique éventuellement substitué lorsque p vaut 2 et W représente le groupe -CO-NH-.
- 15 38. Composé représenté par la formule

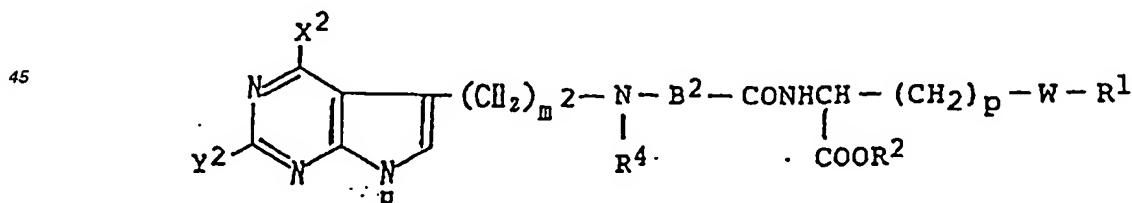


où T représente un atome d'azote, d'oxygène ou de soufre, B¹ est défini comme B dans la revendication 1, X¹ représente un groupe amino hydroxyle ou mercapto, Y¹ est défini comme Y dans la revendication 1, W, R¹ et COOR² sont définis comme dans la revendication 1, m¹ est un nombre entier compris entre 1 et 5, p est un nombre entier compris entre 1 et 4, à condition que p vaille 1, 3 ou 4 lorsque -W-R¹ représente un fragment représenté par la formule suivante :

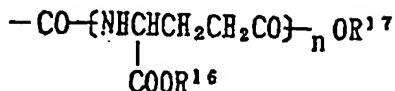


où COOR¹⁶ et COOR¹⁷ sont définis comme dans la revendication 1 et n est un nombre entier compris entre 1 et 5.

- 40 39. Composé représenté par la formule



dans laquelle B² est défini comme B dans la revendication 1, X² représente un groupe amino, hydroxyle ou mercapto, Y² est défini comme Y dans la revendication 1, R¹, R⁴, W et COOR² sont définis comme dans la revendication 1, m² est un nombre entier compris entre 1 et 4, et p est un nombre entier compris entre 1 et 4, à condition que p vaille 1, 3 ou 4 lorsque -W-R¹ représente un fragment représenté par la formule suivante ou le sel correspondant :



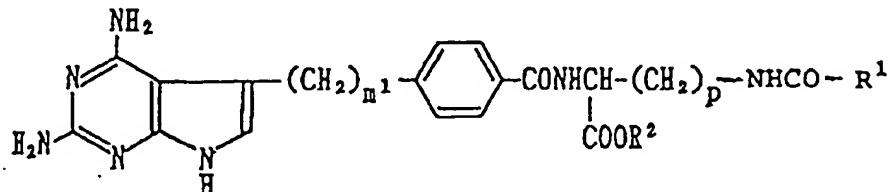
5

où COOR¹⁶ et COOR¹⁷ sont définis comme dans la revendication 1 et n est un nombre entier compris entre 1 et 5.

10

40. Composé conforme à la revendication 1 qui est un composé de formule

15



20

où m¹ représente un nombre entier compris entre 1 et 5, les autres symboles ayant la signification définie dans la revendication 1, ou un sel d'un tel composé.

25

41. Composé conforme à la revendication 40 où R¹ représente un groupe phényle non substitué ou substitué de la manière décrite dans la revendication 1.

30

42. Composé conforme à la revendication 40 où R¹ représente un groupe phényle non substitué ou portant un substituant carboxyl(alkyle en C₁₋₄).

35

43. Composé conforme à la revendication 40 où R¹ représente un groupe naphtyle non substitué ou substitué de la manière décrite dans la revendication 1.

40

44. Composé conforme à la revendication 40 où R¹ représente un groupe naphtyle non substitué ou portant un substituant carboxyl(alkyle en C₁₋₄).

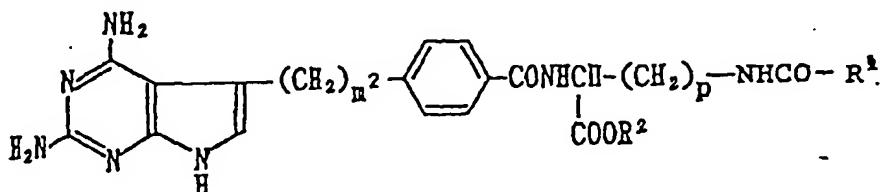
45

45. Composé conforme à la revendication 40 où COOR² représente un groupe carboxyle ou un carboxylate d'alkyle en C₁₋₄.

46. Composé conforme à la revendication 40 où p est un nombre entier compris entre 2 et 4.

50

47. Composé conforme à la revendication 1 qui est un composé de formule



45

dans laquelle m² représente un nombre entier compris entre 1 et 5, les autres symboles étant définis comme dans la revendication 1, ou le sel d'un tel composé.

55

48. Composé conforme à la revendication 47 où R¹ représente un groupe phényle non substitué ou substitué de la manière décrite dans la revendication 1.

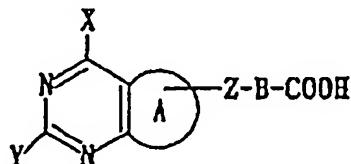
60

49. Composé conforme à la revendication 47 où R¹ représente un groupe phényle non substitué ou portant un substituant carboxy(alkyle en C₁₋₄).

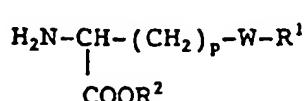
50. Composé conforme à la revendication 47 où R¹ représente un groupe naphtyle non substitué ou substitué de la

manière décrite dans la revendication 1.

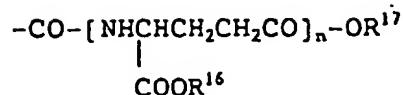
51. Composé conforme à la revendication 47, où R¹ représente un groupe naphtyle non substitué ou portant un substituant carboxy(alkyle en C₁₋₄).
52. Composé conforme à la revendication 47 où COOR² représente un groupe carboxyle ou un carboxylate d'alkyle en C₁₋₄.
53. Composé conforme à la revendication 47 où R¹ représente un groupe tétrazolyle non substitué ou substitué de la manière décrite dans la revendication 1.
54. Composé conforme à la revendication 47 où p représente un nombre entier compris entre 1 et 4.
55. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N(δ)-hémiphtaloyl-L-ornithine ou un sel de ce composé.
56. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N-(3-carboxyphényle)-L-glutamine ou un sel de ce composé.
57. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N(δ)-(3-carboxy-2-naphtoyl)-L-ornithine ou un sel de ce composé.
58. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N(1H-tétrazol-5yl)-L-glutamine ou un sel de ce composé.
59. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N(δ)-hémiphtaloyl-L-ornithine.
60. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N-(3-carboxyphényle)-L-glutamine.
61. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N-(3-carboxyphényle)-L-glutaminate disodique.
62. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N(δ)-(3-carboxy-2-naphtoyl)-L-ornithine.
63. N(α)-[4-[2-(2,4-diamino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)éthyl]benzoyl]-N-(1H-tétrazol-5yl)-L-glutamine.
64. Procédé de préparation d'un composé conforme à la revendication 1, caractérisé en ce que l'on fait réagir un composé de formule



dans laquelle A, B, X, Y et Z sont définis comme dans la revendication 1, ou un sel de type carboxylate réactif d'un tel composé, avec un composé de formule



- ou avec le sel d'un tel composé, dans laquelle W, R¹ et COOR² sont définis dans la revendication 1, et p représente un nombre entier compris entre 1 et 4, à condition que p vaille 1, 3 ou 4 lorsque -W-R¹ représente un fragment représenté par la formule



5

dans laquelle COOR¹⁶ et COOR¹⁷ sont définis comme dans la revendication 1 et n représente un nombre entier compris entre 1 et 5.

10

65. Composition anti-tumorale qui comprend un composé ou le sel d'un composé défini dans la revendication 1.

15

66. Composition anti-tumorale qui comprend une quantité efficace d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé ainsi qu'un véhicule ou excipient pharmaceutiquement acceptable.

20

67. Agent d'inhibition de la prolifération cellulaire comprenant une quantité efficace d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé.

25

68. Agent d'inhibition la prolifération des cellules cancéreuses pulmonaires chez l'homme comprenant une quantité efficace d'un composé conforme à la revendication 1 ou d'un sel pharmaceutiquement acceptable d'un tel composé.

69. Utilisation d'un composé conforme à la revendication 1 ou de son sel pharmaceutiquement acceptable comme composant pour la préparation d'un agent anti-tumoral.

30

35

40

45

50

55